Psychophysical and Brain Activity Assessment of Cold Air Induced Pain

- Exemplified in an in vivo human dental model -

Thesis (cumulative thesis)

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Contents

Abstract

The understanding of neural correlates of a human pain perception has reached an astonishing level since the advent of neuroimaging techniques. Within the last decade, dental pain has come into focus of neuroscientific pain research. Pain assessment and stimulus quality in research plays a pivotal role in order to draw valid conclusions. This thesis aimed at refining bio-psycho-social pain assessment and experimental investigation of dentine hypersensitivity by use of gradable, natural-like stimuli:

Study 1 presents the first freely accessible comprehensive computer-based pain assessment tool, providing bio-psycho-social data acquisition for both clinic and research based on symptom burden and response-driven case finding.

Study 2 presents the development, technical foundation and testing of the world's first application device delivering graded non-contact cold air stimulation on human in vivo teeth in a 3 Tesla MRT-environment (magnetic resonance tomography).

Study 3 incorporates psychophysical cold-air reliability testing of dental perception stability over time (painful vs non-painful states) and shows its challenges and limitations within a subgroup of DH subjects.

These studies present some pioneer work in pain assessment and in the investigation of behaviour and neural correlates of painful somatosensory sensation of trigeminal input by use of intraorally applied and focused, gradable cold air stimuli.

In conclusion, the author's experience during the research process is condensed to six critical claims aiming at a fundamental improvement in neuroscientific pain studies.

Zusammenfassung

Das Verständnis neuraler Korrelate der menschlichen Schmerzwahrnehmung hat seit dem Aufkommen von Bildgebungsverfahren ein erstaunliches Niveau erreicht. Im letzten Jahrzehnt sind Zahnschmerzen in den Fokus der neurowissenschaftlichen Schmerzforschung gerückt. Schmerz-Assessment und Stimulusqualität spielen in der Forschung eine entscheidende Rolle, um valide Schlussfolgerungen zu ziehen. Diese Thesis hat zum Ziel, das biopsychosoziale Schmerz-Assessment zu verfeinern und die Dentin-Überempfindlichkeit (DH) experimentell zu untersuchen:

Studie 1 stellt das erste frei zugängliche computergestützte Schmerz-Assessment-Tool dar, das eine biopsychosoziale Datenerfassung sowohl für die Klinik als auch für die Forschung auf der Grundlage der Symptombelastung und somit eine individuelle Fallanalyse ermöglicht.

Studie 2 präsentiert Entwicklung, technische Grundlagen und Erprobung des weltweit ersten Applikationsgeräts, das abgestufte, berührungslose in vivo Kaltluftstimulation an menschlichen Zähnen in einer 3-Tesla-MRT-Umgebung (Magnetresonanztomographie) ermöglicht.

Studie 3 beinhaltet psychophysikalisches Assessment der Stabilität der Reizwahrnehmung in Zähnen über einen längeren Zeitraum (schmerzhaft versus nicht schmerzhafte Zustände) und zeigt dessen Herausforderungen und Einschränkungen innerhalb einer Untergruppe von DH-Probanden.

Diese Studien präsentieren Pionierarbeit bezüglich Schmerz-Assessment, Untersuchung von Wahrnehmung und der neuralen Korrelate schmerzhafter somatosensorischer Wahrnehmung des Trigeminusnervs durch die Verwendung von intraoral angewendeten und fokussierten, gestuften Kaltluftreizen.
In der Zusammenschau werden die Erfahrungen des Autors während des Forschungsprozesses auf sechs kritische Forderungen kondensiert, die auf eine grundlegende Verbesserung neurowissenschaftlicher Schmerzstudien abzielen.

1 Introduction

The problem of pain, since the beginning of the century, has been dominated by the concept that pain is [but] a sensory experience.

Melzack and Casey 1968

1.1 *The term 'pain': A semantic and taxonomic miscellaneous*

Pain experience, its reliability and neural correlates are the main focus of the studies presented in this synopsis. But initially, a taxonomic outline is presented.
Pain – a term for one of the strongest human motivational systems – seems so lucid at a first glance, because almost every human being has had experiences with it. Looking more closely, this term encompasses various entities of emergence. One basic differentiation of nociception and pain is a basic tripartite taxonomic classification: "Nociception is the physiological process of encoding noxious stimuli, whereas pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." (St John Smith 2018; IASP 1994). Regrettably, this definition often is cited solely, but the International Association of the Study of Pain IASP completes by further crucial aspects:

'The inability to communicate verbally does not negate the possibility that an individual is experiencing pain […] Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an emotional experience. […] Experiences which resemble pain but are not unpleasant, e.g., pricking, should not be called pain. […] Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. […] This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.' (IASP 1994)

IASP-taxonomy specifies: [In a nociceptive process] “pain sensation is not necessarily implied“ (IASP 1994). Another class is neuropathic pain, which is defined as pain caused by a lesion or disease of the somatosensory nervous system. Interestingly, there is no term for the ‘encoding of endogenous noxious processes’ in neuropathic pain, analogue to ‘nociception’, which seems inconsistant out of the taxonomist’s perspective : theoretically, the potential existence of encoding processes even in neuropathic pain before the sensation reaching brain areas cannot systematically encluded.

1.2 *Approaches of pain exploration*

The conceptualization of the term ‘pain’ is approached by different methods and often is not clearly differentiated from the term ‘nociception’. For example on the level of pain genesis by means of molecular (Basbaum et al. 2009) and genetic sciences (Mogil 2012), on the level of perception by quantification of sensation (Nevin 1969; Price et al. 1994), on the level of treatment such as response to pharmacological intervention (Kuijpers et al. 2011) or psychological and behavioral aspects (Morley et al. 1999; Morley und Williams 2015). Clinical guidelines attempt to give precise diagnostical hints and indication for assessment and treatment (AWMF 1962/2018; NICE guidelines 1999/2018), where pain experience is usually outlined by oral elicitation of medical history, clinical examination, imaging, laboratory analysis and questionnaires.

The overview of nociceptive pathways and physiological mechanisms are well and contingently documented and give a specific and fragmented overview of pain processing: Sample images of peripheral and central models of pain processing are provided for instance by Scholz and Woolf (2002), Tracey et al. (2007) Garcia-Larrea and Peyron (2013) and Peyron et al. (2000). Comprehensive overviews of the trigeminal perception system – which is in focus of the following studies - are provided by Da Silva et al. (2002) and Noseda and Burstein (2013).

Technical innovation has allowed the investigation of sensory states of the brain including pain: In the last two decades non-invasive exploration of the human central nervous system which seems to play a major role in pain processing in conscious human subjects has increased significantly by means of magnetic resonance imaging (MRI), positron emission tomography (PET) and even the comparison of different brain states by functional magnetic resonance imaging (fMRI) (Peyron et al. 2000). Near infrared spectroscopy (NIRS) has recently be

used to investigate pain states, even in unborn children (Ferrari und Quaresima 2012; Anand und Hall 2007).

Still, despite precise data that usually emerge after attempts of capturing pain experience in research and clinical setting, the generation of the conscious experience called 'pain' remains a baffling case in major parts. Not least because of inherent properties of the peripheral nervous system and top down modulating mechanisms in the central nervous system, the analysis of painful experience may encounter a serious challenge:
Sensation per se mostly is a result after the integration of a highly complex myriad of endogenous and exogenous inputs. This complexity can present a crucial problem in pain research. One basic example of a challenge, which is taken into account in this thesis' studies, is the interdependence of pain free sensory modalities such as haptics or touch that may bias pain perception in the periphery (Melzack und Wall 1965) or vice versa (Apkarian et al. 2009; Apkarian et al. 2005). This thesis attempts to elucidate some aspects of experimental trigeminal pain, laying the foundations for further studies of somatosensory processes of the central nervous system (CNS).

1.3 *Focus of pain exploration in this thesis*

1.3.1 Computer-based pain assessment in clinical and research setting

As mentioned above, one option of characterizing human pain experience is by written assessment either by paper or computer-based. After decades of paper-pencil assessment (Melzack 1975b), in the beginning of digitalization results of computer-based clinical research retentively suggested some benefit for diagnostics and treatment (Johnston 1994). Currently, a great number of computer-aided pain assessment tools exist, provided by pharmaceutical companies aiming at accurate diagnosis and treatment evaluation. But up to now, none of these tools provide a comprehensive collection and open source use of highly secured data in a bio-psycho-social model including literature- and evidence-based items, applicable in research and the clinical setting.

1.3.2 Experimental pain exploration

In search of a 'pure' pain model, Ettlin, Brügger and Meier focused on the of the trigeminal nerve system by means of experimental tooth stimulation (Brügger et al. 2012; Brügger et al.

2011; Ettlin et al. 2009; Ettlin et al. 2004; Meier et al. 2012) . The tooth's pronounced pain proneness – as most men and women know – seemed ideal to model 'pure' pain. A particularly painful condition in the human tooth is dentin hypersensitivity (DH), a pain which is sharp in character and of short duration, arising from exposed dentin surfaces in response to stimuli such as evaporative and thermal. This pain condition seemed ideal for a human pain model to investigate in otherwise healthy subjects.

As the main method, the research group around Ettlin opted for fMRI as one of the most accurate non-invasive methods of analysing brain responses to potential painful sensory experiences. In the beginnings, vibrotactile (Ettlin et al. 2004) and electrical stimuli (Brügger et al. 2012) were used for event related analysis of fMRI-data. Though, these types of stimuli are quite rare in the everyday experience of the average citizen.
In event related experimental research, the silver bullet to achieve is the maximum of external validity, namely the extent to which the results of a study can be generalized to other (everyday) situations beyond the experimental condition. In order to enhance external validity of the stimulation procedure regarding DH, Meier et al. (2012) employed natural air stimuli at room temperature within the fMRI-Scanner. Besides the everyday valence of an air stimulus another crucial advantage of this stimulus is the absence of tactile or haptical input which may alter pain experience.

Though, recent findings suggest, that some human receptor channels, such as TRPM8, are sensitive to temperature. These channels are also present in the dental nerve (Kim et al. 2014; Alvarado et al. 2007). A large extent of DH patients is especially sensitive to cold stimuli (Bartold 2006), but not to temperatures close to body warmth. As described further below, that was the main gap to close with the experimental setting of this thesis. But firstly, the importance of quantification of sensation has to be emphasized.

Since pain experience is a highly individual process hardly to share with others, quantification is challenging (Craig 2002): Pain perception can be quite steady in chronic pain conditions, but often is a time and event dependent volatile process. The latter is one of the cardinal characteristics in DH patients (Dababneh et al. 1999). Current methods for assessing DH employ non-gradable mechanical and cold stimuli (metal/air/water/ice) and use response scales (Taha und Clarkson 2014), that often rely on subject-investigator interaction that lack validation. In

order to quantify sensation in various qualities, already in the 19th century the relation of stimulus intensity differences and individual sensation within different modalities was investigated, e.g. by G. T. Fechner, one of the founders of psychophysics. He observed in his studies that different individuals have different sensitivity to certain stimuli and then developed the Fechner's law, depicted in *Elemente der Psychophysik 1860* (the subjective sensation is proportional to the logarithm of the stimulus intensity). Today, *quantitative sensory testing* (QST) is the state-of-the-art method for the standardized quantification of sensation: It is a psychophysical method used to quantify somatosensory function in healthy subjects and patients. It is based on measurements of responses to calibrated, graded innocuous or noxious mechanical and thermal stimuli in different modalities (Backonja et al. 2013; Rolke et al. 2006). In classical QST, four parameters are used to characterize responses of Aβ, Aδ and C fibres (Millan 1999): i) Detection of thresholds for innocuous stimuli, ii) Detection of thresholds for noxious stimuli, iii) Pain rating at threshold and at suprathreshold stimulation and iv) Pain induced by repetitive stimulation.

1.3.3 The thesis' main goals

In order to pursue a more scrupulous investigation of human pain experience, two approaches were applied in this thesis:

i) Clinical setting: The development of a computer-based tool applicable for biopsychosocial evaluation in a variety of clinical settings offering direct feedback by a case report summary. The freely available tool enables personalized medicine, facilitates interprofessional education and collaboration, and allows nomothetic data analysis in single and multi center patient-reported outcomes research (study 1).

ii) Experimental exploration of trigeminal pain sensation: In order to investigate central mechanisms of intermittent acute tooth pain in DH patients by use of an externally valid stimulus, an MR- compatible cold air delivery system had to be invented in order to apply graded cold air stimuli to human teeth in the restricted area of a MR-scanner (study 2). Secondly, individual pain thresholds on a sensitive tooth were determined within DH subjects, using QST over a time period of three weeks to check for reliability of perception (Study 3).

2 Empirical studies

2.1 *Empirical study 1*

Design, construction, and technical implementation of a web-based interdisciplinary symptom evaluation (WISE) - a heuristic proposal for orofacial pain and temporomandibular disorders

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Abstract

Background: Medical symptoms independent of body location burden individuals to varying degrees and may require care by more than one expert. Various paper and computer-based tools exist that aim to comprehensively capture data for optimal clinical management and research. Methods: A web-based interdisciplinary symptom evaluation (WISE) was newly designed, constructed, and technically implemented. For worldwide applicability and to avoid copyright infringements, open source software tools and free validated questionnaires available in multiple languages were used. Highly secure data storage limits access strictly to those who use the tool for collecting, storing, and evaluating their data. Concept and implementation is illustrated by a WISE sample tailored for the requirements of a single center in Switzerland providing interdisciplinary care to orofacial pain and temporomandibular disorder patients. Results: By combining a symptom-burden checklist with in-depth questionnaires serving as case-finding instruments, an algorithm was developed that assists in clarifying case complexity and need for targeted expert evaluation. This novel modular approach provides a personalized, response-tailored instrument for the time- and cost-effective collection of symptom-burden focused quantitative data. The tool includes body drawing options and

instructional videos. It is applicable for biopsychosocial evaluation in a variety of clinical settings and offers direct feedback by a case report summary. Conclusions: In clinical practice, the new instrument assists in clarifying case complexity and referral need, based on symptom burden and response –tailored case finding. It provides single-case summary reports from a biopsychosocial perspective and includes graphical symptom maps. Secure, centrally stored data collection of anonymous data is possible. The tool enables personalized medicine, facilitates interprofessional education and collaboration, and allows for multicenter patient-reported outcomes research.

Keywords: personalized medicine, patient-reported outcome measures, orofacial pain, temporomandibular disorders, questionnaire

1. Background

Primary, secondary and tertiary care providers may all be involved in the diagnosis and management of symptoms related to tissue dysfunction and pain disorders. Gathering valid and reliable data in all types of clinical setting is essential for high-quality personalized care and research [1]. Patient self-report data are increasingly recognized as a valuable resource for this purpose. Yet, in the context of patient consultations, it is often difficult to systematically and prospectively collect high-quality data. This aspect is further complicated in studies that aim to comprehensively assess physical and psychosocial parameters, e.g., functionality, pain interference, beliefs and expectations; pain catastrophizing, social roles, functioning, and interactions; emotional distress, and sleep.

The seminal 1992 publication of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) and the subsequent refinement in the form of Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) in 2014 represented a paradigm shift in the evaluation and diagnosis of patients with TMD, a heterogeneous group of disorders affecting the jaw joint and surrounding tissues [2, 3]. The most salient novel feature contrasting with previous TMD diagnostic systems was the introduction of the biopsychosocial model into dental medicine. This concept includes not only the assessment of somatic signs and symptoms (Axis I) but also the biobehavioral domain (Axis II). The screening of patients for psychosocial burdens aimed to appropriately refer patients for expert assessment and interventions to address non-somatic barriers to TMD recovery. Subsequent prospective cohort studies supported the clinical utility of Axis II instruments [4–6]. Psychosocial factors have the potential to affect treatment responses not only of OFP and TMD sufferers, but for many types of chronic pain [7–9]. Management of diverse biopsychosocial issues and/or comorbidities is relevant for some — but not all — individuals experiencing OFP and TMD. Thus, individuals seeking health care vary greatly in their subjective complaints, personal histories, and comorbid conditions. The diverse clinical symptoms of identical pathologies may be attributable to differing environmental, psychosocial, and genetic factors. Common approaches for profiling patients and phenotyping disorders may include the following tools: checklists, questionnaires, interviews, physical examinations, imaging, laboratory tests, and psychological/psychiatric evaluations.

The administration of a barrage of measures can significantly increase patient burden and decrease compliance. Recently, data collection methods that are adapted to a patient's unique history (rather than a lengthy survey including questions that would not apply to them) have become popular [10, 11]. For this purpose, a checklist can call attention to a symptom and ensure that nothing of importance is overlooked. Since multiple somatic and psychological symptoms frequently coexist in OFP and TMD patients, case-finding instruments have been developed for initiating diagnostic procedures that facilitate optimized treatment. For this purpose, cost- and time-effective questionnaires validated in the primary care setting exist that are capable to clarify the need for expert evaluation of individuals possibly suffering from migraine, tinnitus, anxiety, depression, sleep disorders, etc. A possible way to build a tool for comprehensive patient assessment is to combine a symptom-burden oriented checklist with various in-depth questionnaires serving as case-finding instruments.

Traditionally, data collected via paper-based questionnaires can be used for clinical care and research. However, it is time-consuming and costly to extract their data. Paper-based questionnaires are often disliked by patients, data are sometimes unreadable, and missing items are challenging for statistical data analysis [12]. Among others, the US Institute of Medicine advocates using information technology to support patient-centered care and evidence-based decisions [13, 14]. Electronic healthcare records are increasingly implemented in many countries. E.g., in the U.S., a Medicare and Medicaid Electronic Health Care Record Incentive Program was recently established to encourage widespread adoption of an electronic health record [15]. Capturing patient reported information electronically results in a more accurate and complete data set, improved protocol compliance, avoidance of secondary data entry errors, easier implementation of skip patterns, less administrative burden, high respondent acceptance, reduced sample size requirements, and potential cost savings. The increasing number of patients who are already familiar and comfortable with electronic devices are likely to prefer this format of delivery [16]. Health information technology (health IT) enables the collection of large amounts of patient care data in electronic form, but this requires new architectures, techniques, algorithms, and analytics for data management and for extracting knowledge [18]. In the U.S., a collaborative health outcomes information registry (CHOIR) is currently being built from patient data provided by U.S. American care centers [19]. The structure and composition of its questions addressing OFP and TMD, its algorithm, and its scoring system are, however, not publicly available.

The goal of this project was to design, construct, and implement a modular, universally accessible, web-based instrument for interdisciplinary symptom evaluation (WISE) for subject-tailored assessment of OFP and TMD prior to clinical interviews. We aimed to clarify symptom-burden by a checklist and with case-finding instruments in the form of publicly available, in-depth questionnaires to create response-tailored assessments. Copyright issues were avoided and a highly secure data storage location free of third party interests was selected.

2. Methods and materials

2.1. Open source software tools

2.1.1. LimeSurvey™ (LS)

To design and construct the WISE for OFP and TMD, we used LimeSurvey™ 2.05+ (150310), which is a platform-independent open source framework for the development of internet based surveys [20]. LS runs on any web server and the data is stored in a MySql database. To ensure privacy, data can be transmitted via secure https. As a survey framework, LS contains predefined response formats including single and multiple choice, array responses, and equations. Equations enable calculation of scores that serve as filters to stratify for additional in-depth questions. LS implements the construction of multilingual surveys. Data can be exported in different formats, such as SPSS, Excel, and others.

2.1.2. ImageMapster (IM)

IM is a JQuery-based tool for using image maps for data entry [21]. Predefined areas of a background image can be selected to graphically represent pain on a body schematic. IM can easily be included in the LS question code. In the WISE for OFP and TMD, IM was used for the assessment of OFP location and severity.

2.2. Data security and storage

Maintaining participant privacy is critical. The WISE for OFP and TMD can run on any highly secure webserver. Data security and storage can be managed in a single country or on widespread servers. For optimal data security, data linked to patient identity are stored independent of survey data. The latter are stored in anonymized form on a highly secure central server, whereas patient identity data are stored locally in clinics or centers. Single-case summary

reports are generated by linking local and central data via a unique identification number (ID). In this process, the only data exchanged is an anonymous ID and anonymized survey data (SDATA). During initial data collection, the authors managing patients at the Orofacial Pain Unit of the Center of Dental Medicine, University of Zurich (UZH) established a central secure host at Service and Support for Science IT of the UZH, adhering to Swiss federal and cantonal laws for privacy protection. Figure 1 illustrates the current setup at the University of Zurich, Switzerland.

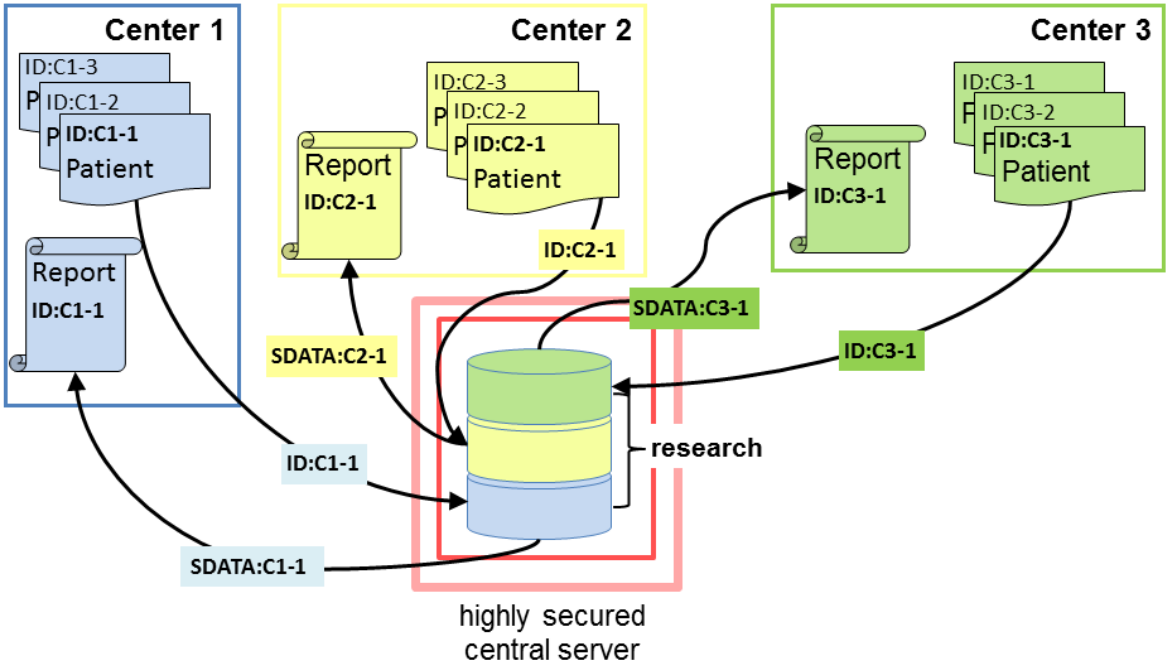

Fig. 1. Overview of data exchange options between multiple patient management centers and a secure central data collection server. For clinical practice, customized single case reports available only to the supplying clinic are generated from centrally stored data that are linked by a unique identification number (ID). For research purposes, anonymized data clusters can be merged, thus enabling multicenter research projects.

2.3. WISE concept, structure and content

The WISE was designed to assist clinical decision making. A key requirement was the ability to capture symptoms that are commonly experienced by patients reporting to a given health care provider setting. In order to illustrate the pragmatic implementation of this technical tool and its underlying concept, we present a WISE sample structure tailored for the requirements

of the interdisciplinary orofacial pain unit at the University of Zurich, Switzerland, where patients seek care for a broad variety of musculoskeletal, neuropathic and idiopathic orofacial pains conditions. From a technical-methodological perspective, adapting the software to satisfy various content requirements of similar or other settings is easily accomplished owing to the tool's modular and modifiable design.

Conceptually, the WISE was structured to assess patients in three stages: 1) assessment of symptom burden by a checklist, 2) response-tailored in-depth analyses of burdening symptoms by case-finding validated questionnaires, and 3) targeted expert evaluation(s) of burdening symptoms identified as likely being part of a defined condition.

Importantly, the term "symptom" relates to the subjective experience of an unusual state (abnormal function or feeling) that is not directly measurable. Making perceptual decisions and classifying bodily sensations as possibly harmful is an inherent part of interoception which influences the subjective experience of symptom-related burden [22]. E.g. a headache may be painful, but perhaps not sufficiently burdening the person to take medication. Analogously, a jaw joint sound due to an anterior disc displacement with reduction may be slightly annoying to some people, yet highly burdening to others. Uncertainty about the harmfulness of bodily sensations typically influences the individually perceived symptom burden [23]. It is for these reasons that the WISE checklist focuses on degree of somatic and psychological symptom burdens. Whether burdening symptoms are part of an expert defined condition can be further evaluated by in-depth questionnaires which serve as validated case-finding instruments for clarification. Clinicians are thereby alerted about the possible indication for further interdisciplinary expert evaluation The latter may involve more refined validated instruments such as e.g. a structured clinical interview and/or validated clinic assessment for establishing a diagnosis according to DC/TMD, International Classification of Headache Disorders, Diagnostic and Statistical Manual of Mental Disorders, etc.

2.3.1. Questionnaires by which checklist content was thematically aligned

Co-existence of multiple somatic and psychological symptoms is prevalent in OFP and TMD patients. For heuristic purposes, the item content of the WISE symptom burden checklist was thematically aligned with questionnaires commonly addressing these diverse symptom domains. Notably, the adaptation of items and/or of entire questionnaires resulted in the loss of

their originally validated psychometric properties. The symptom burden checklist items were taken as is or adapted from the following instruments.

2.3.1.1. DC-TMD Symptom Questionnaire (DC-TMD-SQ)

The DC-TMD-SQ has 14 items and is part of the DC/TMD algorithms, the validity of which is presented in Schiffman et al. [3].It inquires about the presence of common symptoms associated with OFP and TMD..

2.3.1.2. Patient Health Questionnaire 15 (PHQ-15)

The PHQ-15 evaluates the severity of somatic symptoms [25]. It was never intended to diagnose a specific clinical entity.

2.3.1.3. PHQ-Stress

PHQ-Stress is a 10-item subscale of the Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire that addresses burden by psychosocial stress [26].

2.3.2. Validated case-finding questionnaires

The following questionnaires clarify whether burdening symptoms are part of an expert defined condition and thus assist clinicians in identifying patients that might benefit from further targeted expert evaluation. Information on their coefficient alpha and test-retest reliability has been included when published.

2.3.2.1. Patient Health Questionnaire 4 (PHQ-4)

The PHQ-4 screens for anxiety and depression in primary care patients [27, 28]. It consists of two subscales GAD-2 (item 1 and 2 of the General Anxiety Disorder Questionnaire 7) and PHQ-2 (item 1 and 2 of the Patient Health Questionnaire 9). Items are scored on a four-point ordinal rating scale. Scores can be calculated for the two subscales (maximum score = 6) as well as overall (maximum score = 12). Total scores of 6 to 8 or subscale scores of 3 to 4, respectively, indicate a *possible* disorder (“yellow flag”). Total scores above 8 or subscale scores above 4, respectively, are suggestive of a *probable* disorder (“red flag”). The following coefficient alpha have been reported: PHQ-4: 0.87; PHQ-2: 0.75; GAD-2: 0.82 [27], and for test-retest reliability: PHQ-4: 0.81; PHQ-2: 0.77; GAD-2: 0.69 [29].

2.3.2.2. General Anxiety Disorder Screener 7(GAD-7)

The GAD-7 assesses general anxiety in primary care patients [30, 31]. High correlations with disability measures were found [32]. Seven items covering different aspects of general anxiety are scored (using the same scale as the PHQ-4). Summary scores range from 0 to 21 and indicate anxiety levels of “none/minimal” (0–4), “mild” (5–9), “moderate” (10–14), or “severe” (> 14). The following coefficient alpha has been reported: 0.92 and fortest-retest reliability: 0.83 [33].

2.3.2.3. Patient Health Questionnaire 9 (PHQ-9)

The PHQ-9 assesses severity of depression [34]. Like the GAD-7, it correlates with functional impairment [32]. Nine items covering different aspects of depression are scored (using the same scale as the PHQ-4). Summary scores range from 0 to 27, indicating depression levels of “none/minimal” (0–4), “mild” (5–9), “moderate” (10–14), “moderately severe” (15–19), or “severe” (> 19). A cut-off score range of 8–11 has been recommended for expert evaluation referral [35, 36]. The following coefficient alpha has been reported: 0.89 and for test-retest reliability: 0.84.

2.3.2.4. PHQ-Stress

The cut-off scores are 10 for “medium” and >14 for “severe” burden by psychosocial stress [26]. No coefficient alpha nor test-retest reliability were reported.

2.3.2.5. Graded Chronic Pain Scale (GCPS) v2

The GCPS was originally developed for general population surveys and primary health care to improve prognostic categorization and treatment decisions [37]. Its prognostic validity in OFP and TMD research has been supported: Higher GCPS ratings are a risk factor for pain chronicity [4]. For clinical decision-making, matching TMD pain-related disability levels with appropriate treatment has been recommended [38]. GCPS consists of seven items measuring pain intensity and related disability, which were scored independently. The maximum disability score is 6. Scores of 3–4 are interpreted as moderate impairment and 5–6 as severe impairment. The 90 days version of the scale was implemented for the WISE. The following coefficient alpha has been reported: 0.71 for TMD pain, test-retest reliability has not been reported.

2.3.2.6. Pain Catastrophizing Scale (PCS)

The PCS assesses catastrophizing thoughts and corresponding behavior [39]. Its 13 items were rated on a 5-point ordinal rating scale. The maximum score is 52, with a cut-off score of 30 [39]. The following coefficient alpha has been reported: 0.87 and for test-retest reliability: 0.75.

2.3.2.7. Insomnia Severity Index (ISI)

The ISI screens for sleep disorders by measuring the severity of insomnia problems, sleep-related satisfaction, and interference. Items were rated on a 5-point ordinal rating scale. The maximum score is 28, with a cut-off score of 14 [40–43]. The following coefficient alpha has been reported: 0.74, test-retest reliability was not reported.

2.3.2.8. Brief Illness Perception Questionnaire (B-IPQ)

The B-IPQ assesses cognitive and emotional representations of illness and health threat [44, 45]. Eight questions covering different aspects of illness perception were rated on a numeric rating scale ranging from 0 to 10. No cut-off score has been reported. Test-retest reliability of the single items of the B-IPQ range from .48 to .70, a coefficient alpha value was not reported.

2.3.2.9. Injustice Experience Questionnaire (IEQ)

The IEQ assesses injustice experienced due to accidents, injuries, or maltreatment [46]. Twelve items, which reflect the frequency of thoughts, beliefs, and emotions associated with injury, were rated on an ordinal scale ranging from 0 to 4. The maximum score is 48, with a cut off score of 30 representing a clinically relevant level of perceived injustice [32]. The following coefficient alpha has been reported: 0.92 and for test-retest reliability: 0.90.

2.3.2.10. Dysmorphic Concern Questionnaire (DCQ)

The DCQ assesses excessive preoccupation with imagined or actual, minimal defects in appearance that significantly influence psychosocial functioning [47, 48]. It consists of seven items, rated on an ordinal scale ranging from 0 to 3. The maximum score is 21 with cut off

score of 9 suggesting a possible body dysmorphic disorder [47]. The following coefficient alpha for the DCQ has been reported: 0.85, test-retest reliability was not reported.

2.3.2.11. Tinnitus Handicap Inventory (THI-12)

The 12-item THI assesses tinnitus severity and its impact on daily life [51]. The summary score ranges from 0 to 24 indicating following levels of impairment by tinnitus: 0–6 denotes "*no handicap*", 7–10 "*mild handicap*", 11–14 "*moderate handicap*", and >14 "*severe handicap*". The following coefficient alpha has been reported: 0.88 and for test-retest reliability: 0.89.

2.3.2.12. Identification of Migraine (ID-Migraine™) screener

The three-item ID-Migraine™ screens for migraine headache [52, 53]. An affirmative response to two of three items discriminates migraine from other headaches. No coefficient alpha or test-retest reliability was reported for this instrument.

2.3.3. Other symptom exploration instruments

2.3.3.1. Jaw Function Questionnaire (JFQ)

The JFQ is a checklist of 12 daily jaw activities for assessing OFP and TMD related disability [49]. It was part of an earlier version of instruments to assess axis-II disorders of the RDC/TMD consortium. It was preferred over the Jaw Function Limitation Scale because the latter contains items unsuitable for vegetarians/vegans, leading to cultural bias. The answer options were expanded to "*no*" (=0), "*a little*" (=1), and "*a lot*" (=2) to better assess the impact of limitations. No diagnostic cut-off value applies. We added two measures for quantitative evaluation: 1) "jaw function" on a scale ranging from "*normal function*" (0) to "*no movement possible*" (10) and 2) "dietary restrictions" on a scale ranging from "*no restrictions*" (0) to "*liquid only*" (10) [50].

2.3.3.4. Somatosensory symptom checklist (SSC)

Somatosensory facial alterations are not systematically captured in orofacial pain questionnaires. For the WISE for OFPand TMD, we integrated an eight-item checklist that is used to assess posttraumatic neurosensory deficits or altered function [54]. No cut-off value applies.

2.4. Administration

After receiving a referral email or letter, the clinic administrator registers the patient in a database. The login information for the WISE for OFP and TMD is sent to the patient by letter. Upon opening the survey, patients receive information about its purpose, duration, and privacy protection. Instructions, including short video-clips, are available for assistance. Upon submitting the questionnaire, a patient will be contacted by the clinic administration in order to schedule an appointment. This is the way that our clinic uses the WISE, but any different implementation is possible.

3. Results

Similar to a patient chart, the WISE for OFP and TMD captures information according to the following structure:

1) General information / patient characteristics (gender, age, height, weight, known allergies, social and parafunctional habits, primary care and referring clinician, occupational status);

2) Chief complaint(s) and modulating factors;

3) Symptom burden checklist and related in-depth questionnaires;

4) Previous diagnoses and effects of prior treatments;

5) Privacy policy, informed consent.

3.1. . General structure and scoring of the symptom burden checklist

The checklist begins with items addressing symptom burden in various extra- and intraoral locations. Additional checklist items were included for comprehensive orofacial symptom assessment such as xerostomia, halitosis, dysphagia, tooth/jaw related dysmorphophobia, and obstructive sleep apnea. Pain-related questions were grouped by body areas. Checklist-item scoring was structured according to the PHQ-15 by grading the symptom-related burden.

3.2. Thresholds for presenting case-finding tools and in-depth questions

Thresholds for presenting case-finding tools and in-depth questions can be adjusted, depending on particular clinic or research focus. Here, we suggest a low threshold for pain-related

checklist items and a higher threshold for others. I.e., patients who check being bothered at least 'a little' for one or more pain items were offered additional in-depth questions which focus on capturing graphically pain location and intensity in the following areas: head/face, torso, and elsewhere on the body. Further questions address pain quality, onset, duration, time pattern, diurnal course, and pain-related disability (Table 2 and section 3.4.1.). The threshold is set to 'bothered a lot' for the presentation of the following case-finding tools: PHQ-9, GAD-7, IPQ, PCS, DCQ, IEQ, PHQ-S, THI-12, ISI.

3.3. Assembly of the WISE items (see Table 2)

3.3.1. DC-TMD Symptom Questionnaire (DC-TMD-SQ)

The DC-TMD-SQ consists of checklist items (items 1, 5, 8, 9, 13) and related in-depth sub items (items 2, 3, 4, 6, 7, 10, 11, 14). .

Content of DC-TMD-SQ item 1 (pain in the jaw, temple, in the ear, or in front of the ear) was split into checklist items 2 and 3. Content of DC-TMD-SQ items 5 (headache) and 8 (joint noises) were added unaltered to the checklist. Content of DC-TMD-SQ item 9 (closed locking of the jaw) and item 13 (open locking of the jaw) were grouped into checklist item 5. The recall period for symptom presence was limited to 30 days, consistent with other checklist items.

The content of DC-TMD-SQ items 2, 3, and 6 were placed in the in-depth pain exploration section (see section 3.4.3. and 3.4.4). Content of DC-TMD-SQ sub items 4 and 7 were covered in the JFQ, which focuses on disabling rather than aggravating aspects of OFP and TMD. Finally, content of DC-TMD-SQ sub items 10, 11 and 14 (corresponding to DC-TMD-SQ checklist items 9 and 13) were omitted because these aspects were considered better explored in the clinical interview.

3.3.2. Patient Health Questionnaire 15 (PHQ-15)

In OFP and TMD sufferers somatization is prevalent in primary care [55]. Importantly, the PHQ-15 items were not used as a measure of somatization severity according to its original publication [32]. Rather than using the PHQ-15 as a validated questionnaire, its item content was included in the checklist to coarsely assess the burden of physical / bodily symptoms beyond OFP AND TMD (see Table 1). E.g., content of PHQ-15 items 1 (stomach pain), 4 (menstrual cramps or other problems with your periods), 6 (chest pain), and 11 (pain during sexual intercourse or other sexual problems) were slightly

modified to focus on pain and grouped into checklist item 13. Content of PHQ-15 items 7 (dizziness), 8 (fainting spells), 9 (feeling your heart pound or race), 10 (shortness of breath), and 13 (nausea, indigestion) were grouped into WISE checklist item 18, to screen for symptoms associated with autonomic dysfunction. PHQ-15 item "trouble sleeping" was replaced by content of item 3 of PHQ-9 item "trouble falling or staying asleep, or sleeping too much." Because of the analogous scoring, it was placed after the PHQ-4 section in the checklist. We considered the PHQ-9 item content more appropriate since it covers a broader spectrum of sleep problems.

3.3.3. PHQ-Stress

The content of PHQ-Stress items were transformed into checklist items, to screen for psychosocial stressors. Content of PHQ-Stress item 2 (your weight or how you look) was covered by checklist items 8 and 16. Content of PHQ-Stress item 3 (little or no sexual desire or pleasure during sex) was covered by checklist item 13. Content of PHQ-Stress items 5 (stress of taking care of children, parents, or other family members), 6 (stress at work outside of the home or at school), and 7 (financial problems or worries) were grouped into checklist item 19. Content of PHQ-Stress items 4 (interpersonal conflicts) and 8 (lack of support / loneliness) were grouped into checklist item 20. Content of PHQ-Stress items 9 (something bad that happened recently) and 10 (thinking or dreaming about something terrible that happened to you in the past) were grouped into checklist item 22. Content of items 2 and 3 were not integrated into checklist because their content was already covered by other checklist items.

3.3.4. Patient Health Questionnaire 4 (PHQ-4)

The PHQ-4 was implemented in its original version, except that the recall period was adapted to "over the last 30 days," for covering the same time interval in all WISE assessments. The sleep item of PHQ-9 was added below the PHQ-4 due to the analogous scoring.

3.3.5. Optional checklist items

Patients experiencing ongoing pain associated with invasive procedures may experience feelings of injustice. Additionally, some patients may feel that they are a burden to others. For screening purposes, these aspects were captured by the two items listed in Table 4.

Depending on the needs of a given clinic or research focus, additional items can be included. In addition to the items listed in Table 4, further examples are listed in Table 2 (items 10, 11, 17 and 21).

3.4. Pain related in-depth questions

Upon exceeding a predefined checklist threshold value , the following items were presented.

3.4.1. Pain severity and location

Various tools measure pain severity. We chose the NIH Toolbox as it is widely accepted. It uses an eleven-point intensity rating scale with anchors 0 (“no pain”) and 10 (“worst imaginable pain”) [56]. For consistency, we implemented these anchors in the entire WISE for OFP and TMD.

For different regions of the head, face, and mouth, pain intensity during the last 4 weeks was assessed using a pain-drawing tool. On an image of the head and oral cavity, predefined regions relating to underlying anatomical structures could be selected with a mouse-click (e.g., masticatory muscles, teeth; Fig. 2). IM was used to make these areas selectable and to color selected regions, with darker red denoting greater pain intensity. Patients first click on the area of the most burdensome pain, which revealed a dialog querying the most frequent pain intensity at rest and maximum pain intensity on jaw movement.

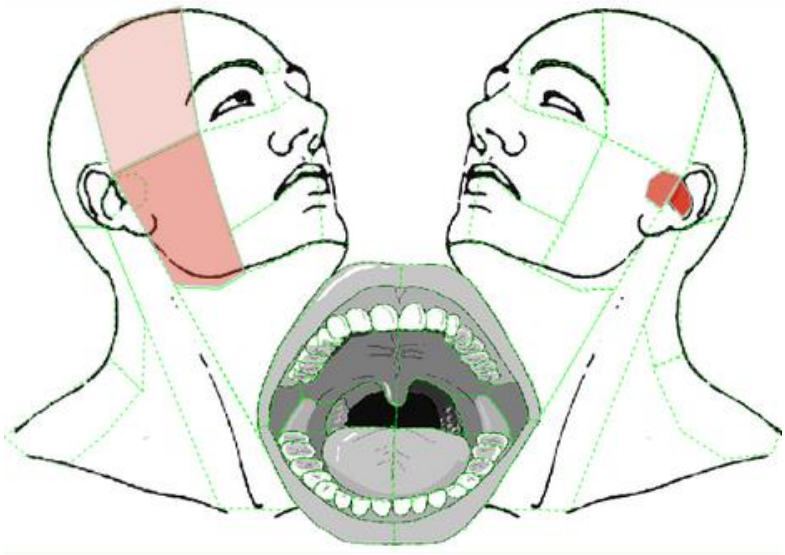

Fig. 2. Pain drawing. The predefined areas are marked with green dotted lines. Pain intensity of selected regions is represented by gradients of red. Darker red indicates more intense pain.

3.4.2. Pain quality

Pain quality was characterized by the descriptors (Schmerzbeschreibungsliste; SBL) of the German pain questionnaire (Deutscher Schmerzfragebogen; GPQ). The list was supplemented with adjectives that capture distinct OFP perceptions [57, 58]. Patients were requested to choose which of 15 pain descriptors described their typical current pain and pain at illness onset. The list included nine sensory pain adjectives ("dull-pressing," "pulling," "stinging," "pulsating-throbbing," "burning-hot," "pins and needles," "shooting-electric," "tingling," "numb") and six affective pain adjectives ("dreadful-horrible," "miserable-atrocious," "exhausting," "grueling," "agonizing," "frightening"). The option "other pain quality" allowed patients to add descriptors that were otherwise not covered.

3.4.3. Pain duration

Because the time value that defines chronic pain varies from 3 to 6 months, we added an interval ranging from 3 to 6 months to the classification used in the GPQ [57, 59]. We included the following time intervals: *"up to 3 months*," *"more than 3 up to 6 months*," *"more than 6 months up to 2 years*," *"more than 2 years up to 5 years*," and *"more than 5 years*."

3.4.4. Time pattern

For the most burdensome pain, time variation was assessed by one of four different patterns, according to the GPQ [57] (Fig. 3). Patients chose the time pattern that best matched their typical pain course. If pattern 2, 3, or 4 was chosen, the following item was presented: "Please indicate the intensity of the most frequent maximum pain during the last 4 weeks." Choosing pattern 3 or 4 was followed by the items: "How often do these attacks typically occur while awake? (number of attacks per 24 hours)", "How often do these attacks typically occur while sleeping? (number of attacks per 24 hours)", "Which is the typical duration of your attacks?" and "The attacks are triggered by …?".

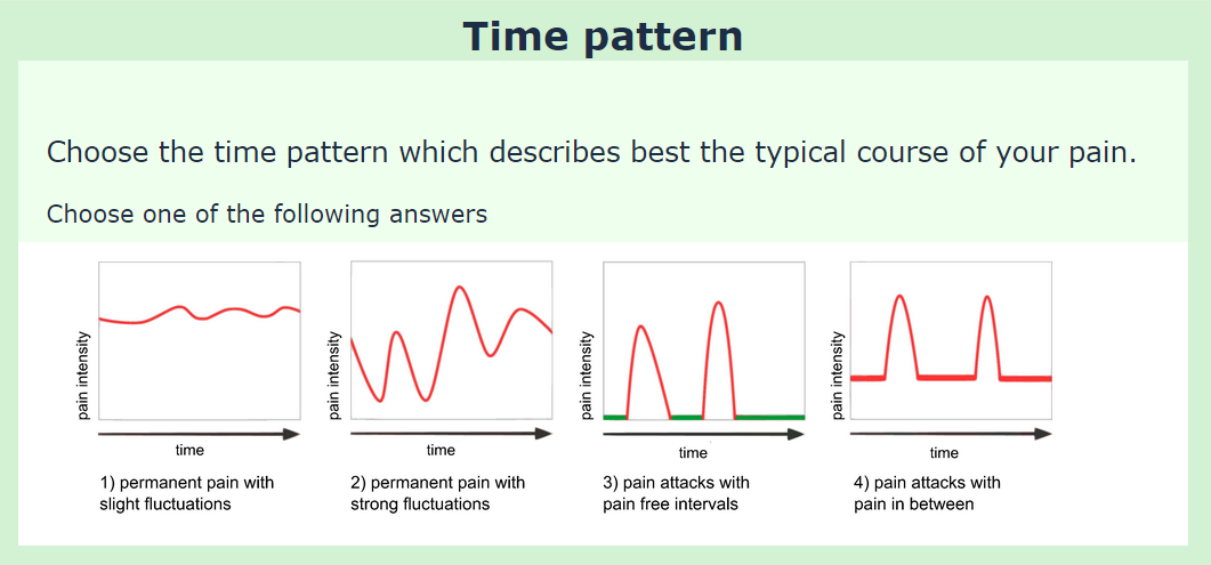

Fig. 3. Time pattern of pain. Patients can select one of four different patterns.

3.4.5. Diurnal pain course

For the most burdensome pain, seven sliders were used to represent the most frequently experienced intensity during three-hour intervals throughout the day and one six-hour interval at night (Fig. 4). Because maximum pain severity was already captured in section 3.4.1. (Fig. 2), the “most frequent” pain was considered more relevant in this context. The ill-defined term “average” pain intensity was intentionally avoided.

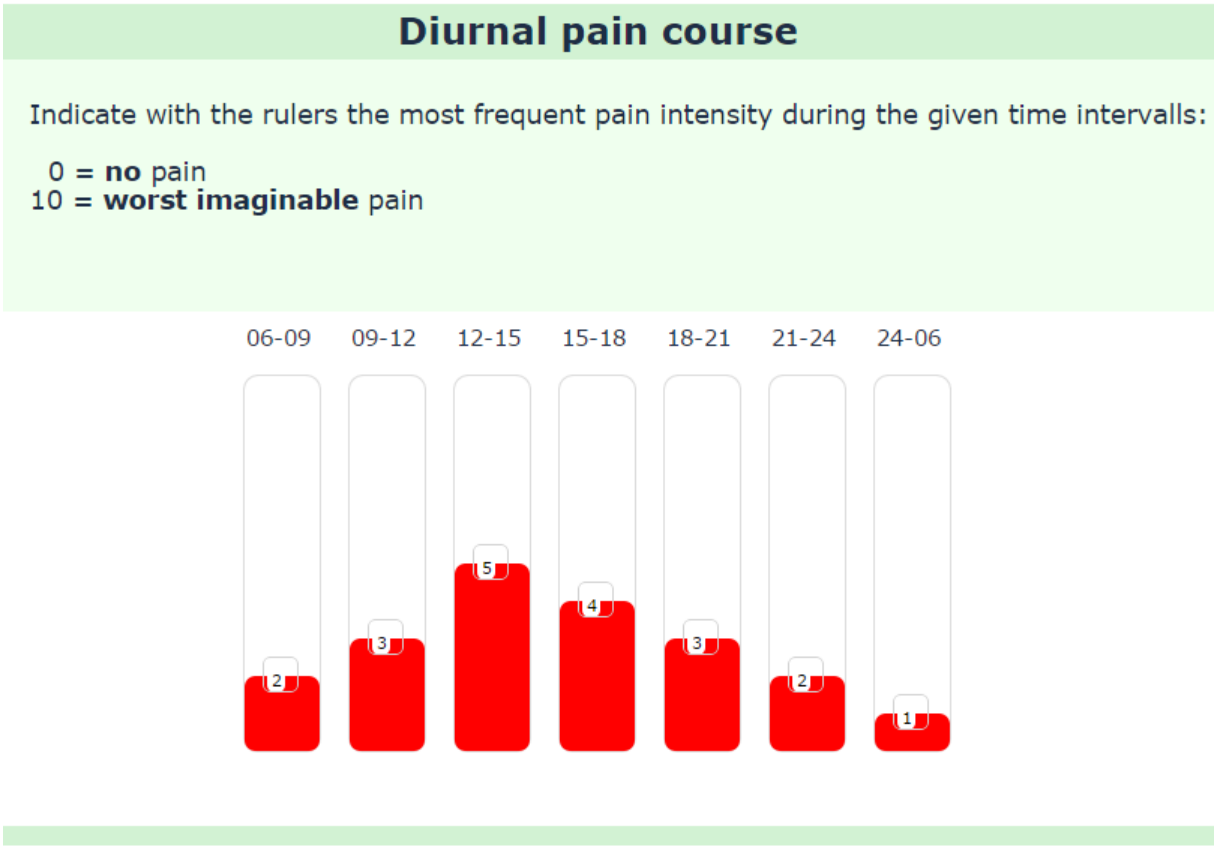

Fig. 4. Example of a possible diurnal pain course. Each bar represents a 3-hour time period during the day and a six-hour period at night. Most frequent pain intensity from 0 to 10 is indicated by moving the bars accordingly.

3.4.6. Onset of pain

Possible reasons for the onset of pain were captured by a single-choice checklist with the options a) "gradual," b) "sudden," c) "by event (accident, physical/emotional stress, dental/medical treatment, operation, illness)," and d) "other." If applicable, further sub-items explored the date of first memorable occurrence and the exact nature of events.

3.5. Single case summary report

Single case summary reports varied in length, depending on case complexity. We present two examples of the computer-generated data assembly in Figs. 5 and 6. Note that the report is interactive. Detailed results of in-depth questionnaires can be displayed by moving the cursor over selected areas of images or over the ⓘ button.

3.6. Language options

Multilingual surveys are optional in LS.

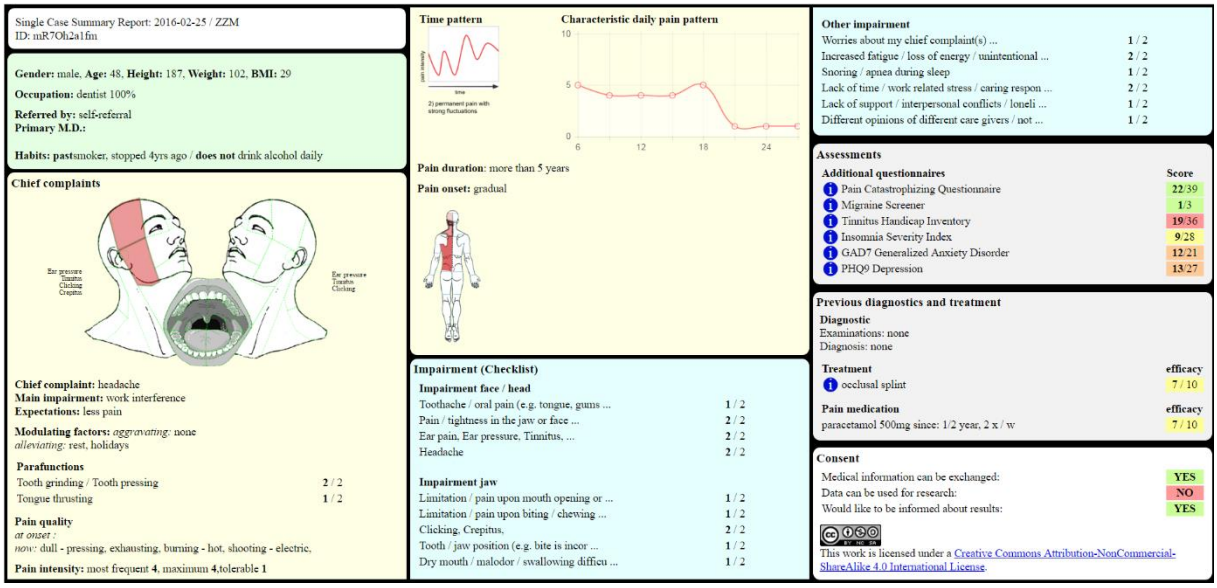

Fig. 5 Example of a single case summary report

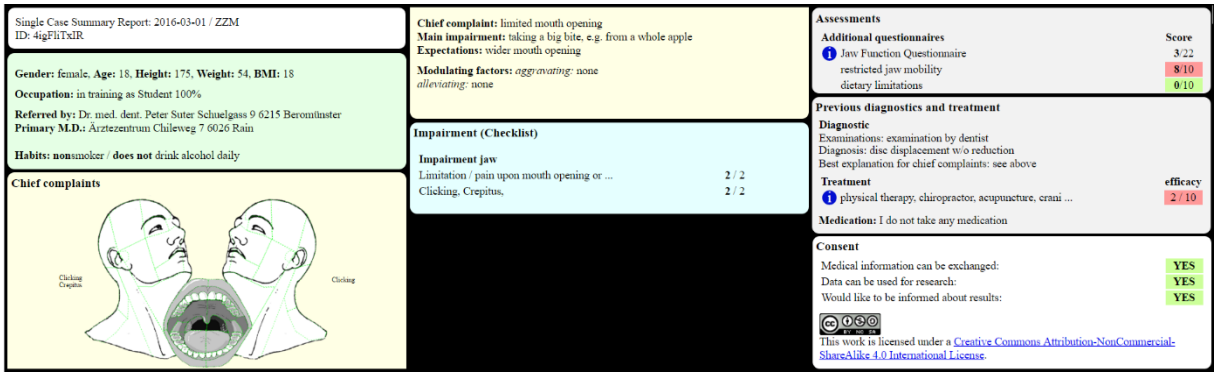

Fig. 6. Example of a single case summary report

4. Discussion

Francis W. Peabody opined that “the secret of the care of the patient is in caring for the patient” [60]. Today, health IT offers new ways of identifying patient needs by comprehensively assessing the varied biopsychosocial factors that influence the experience of pain and other symptoms. From a conceptual point of view, the WISE prioritizes the subjective symptom burden. Many symptoms in the orofacial regions differentially burden individuals such as jaw

joint noises, feeling of tension in the masticatory muscles, C-shaped jaw deviation, etc. Whereas they are barely bothersome to some people, they can be majorly burdening to others. This experiential disparity is often linked to psychological comorbidities unidentified in the primary (dental) care setting. In many everyday clinical situations, patient management will be symptom oriented and the indication for interdisciplinary (e.g. psychological) evaluation will depend mostly on symptom burden. Commonly the therapeutic strategy for patients suffering from musculoskeletal, neuropathic or idiopathic pain in the orofacial region is targeted towards symptom relieve rather than elimination of etiologic factors as these are often unknown. Thus, the WISE supports clinical decision making in clinical practice aiming at identifying patients' needs (based on symptom burden) for optimal care, possibly including an interdisciplinary approach.

The scoring of WISE checklist items focuses on symptom-related burden, per J. D. Loeser: "It is suffering, not pain, that brings patients into doctor's offices in hopes of finding relief" [62]. Besides diagnostic performance, questionnaires are ideally brief, self-administered, multipurpose, free, and easy to score. All these features were considered in generating the WISE.

We described in detail the design, construction, and technical implementation of web-based questionnaire for assessing patients with OFP and TMD. It was designed to be modular, flexible, extensible, and to include drawing options as well as instructional videos. The use of open-source software tools and freely available questionnaires prevented copyright infringements. Secure data storage limits access strictly to those who use the WISE for collecting, storing, and evaluating their own data. Although WISE and the US-based CHOIR have similarities, no available manuscript reports on the structure and composition of its OFP andTMD questions, its algorithm, or its scoring system [19].

For patients, a major advantage is that the WISE is available independent of location; therefore respondents can provide information without time pressure via any available computer, on all possible platforms, using any standard browser, and in different languages. The WISE's modular design is highly patient-centered as it enables personalized assessment of biopsychosocial burden. The option to stop and restart at any point in time diminishes the cognitive burden and respondents can easily review and revise entered data before submission. Respondents are not dependent upon planned, prearranged clinical appointments.

For care providers and administrative personnel, the WISE is easy to administer and electronic data are stored securely. The system can even be used by clinicians who lack electronic health records. The tool's modular structure enables organization of relevant information prior to patient appointments, thus facilitating time and personnel management. Namely, information on somatic and psychosocial burdens may clarify the need for interdisciplinary consultation to identify an appropriate expert. The single case summary report of WISE enables a focused clinical evaluation that prioritizes the most burdensome complaints. This likely facilitates care-giver-patient interactions as from the outset the patient feels understood regarding his/her chief complaint.

For educators, the WISE can assist interprofessional education (IPE) in this field [64]. IPE aims to share skills and knowledge among health care disciplines. WISE case reports in a teaching environment can illustrate to students benefits to patients of working within interprofessional teams [65]. Implementation of such educational models has been recommended by the Institute of Medicine of the US National Academies [66].

Clinical researchers benefit from the WISE by having available standardized data sources. A database is generated without the need for cumbersome transcription of paper-based tools. Central data storage allow for prospective data collection and aggregation from different centers. Novel study designs can be initiated that overcome limitations of conventional randomized controlled clinical trials, e.g., comparative (real world) effectiveness studies [67–70]. Biopsychosocial phenotypes identified through research can be used in clinical practice for more refined screening and more tailored management [71].

For health insurance carriers and other third-party financing agents, personalized health contributes directly to cost savings, but also indirectly by reducing the risk of chronicity.

Finally, wide implementation of the WISE will aid to adequately and comprehensibly incorporate psychosocial entities in classification systems rooted in an ontological framework based on analysis of symptom clusters [61, 72–76].

The WISE is extensible: the composition of symptom burden checklist items and/or case finding instruments can be modified, depending on the needs of a given clinic, e.g., for more detailed exploration of obstructive sleep apnea, halitosis, xerostomia, dysphagia, etc.

4.1. Limitations

There are limitations of web-based instruments: Compared to paper-based versions, completing electronic questionnaires is more time consuming and some people may require assistance. With increasing familiarity with electronic devices, this problem will likely diminish. In the context of clinical trials, most patients prefer electronic data collection methods [16]. Whether the web-based administration significantly decreases patient burden and increases compliance will require further evaluation.

In this paper, the WISE symptom domains were selected for a single interdisciplinary OFP and TMD care team in Zurich. Future studies are warranted to clarify the validity of the chosen symptom burden checklist structure. We opted for the above mentioned case-finding questionnaires based on the following priority sequence: free availability > brevity> robust psychometric properties in the primary care setting. This choice was an arbitrary decision by the authors and not based on an international expert panel recommendation.

The WISE was designed to assist clinical decision making. Whether it also has psychometric validity requires further testing. Also, determination of the optimal thresholds for opening a case-finding instrument needs further clarification. Further, the utility of the instrument to detect change over time for determining treatment effects will need to be clarified. Our planned future research will focus on these issues.

The current version of the WISE uses seven vertical rulers for obtaining a general impression of the diurnal pain course. This is a common limitation of electronic data gathering compared to a pencil-paper approach where pain courses can easily be drawn. Also fluctuating pain patterns cannot be captured by this tool. Still, we estimate that the combination of the diurnal pain course combined with the general pain pattern will offer an initial impression of most clinically relevant pain patterns. However, this assumption will require future scientific assessment.

The WISE for OFP and TMD is only one part of an integral patient evaluation that also includes an interview, physical examination, imaging, laboratory tests, other expert evaluations, etc. How all these additional data can be integrated in a comprehensive patient database remains to be explored.

5. Conclusions

The WISE for OFP and TMD is a novel web-based tool that assists clinicians in clarifying case complexity and referral need, based on symptom burden and response –tailored case finding. It provides single-case summary reports from a biopsychosocial perspective and includes graphical symptom maps. Secure, centrally stored data collection of anonymous data is possible. The tool enables personalized medicine, facilitates interprofessional education and collaboration, and allows for multicenter patient-reported outcomes research.

6. Summary

We presented the design, construction, and technical implementation of a web-based instrument for interdisciplinary evaluation of symptom burden, illustrated for OFP and TMD.

7. Declarations

8. List of abbreviations

B-IPQ Brief Illness Perception Questionnaire

CHOIR Collaborative health outcomes information registry

DCQ Dysmorphic Concern Questionnaire

DC-TMD Diagnostic criteria for temporomandibular disorders

DC-TMD-SQ DC-TMD Symptom Questionnaire

GAD-2 short form of the General Anxiety Disorder Questionnaire 7

GAD-7 General Anxiety Disorder Screener

GCPS Graded Chronic Pain Scale v2

GPQ Deutscher Schmerzfragebogen

ID Identification number

ID-Migraine™ Identification of Migraine

IEQ Injustice Experience Questionnaire

IM Image Mapster

ISI Insomnia Severity Index

IT Information Technology

JFQ Jaw Function Questionnaire

LS LimeSurvey

OFP Orofacial Pain

PCS Pain Catastrophizing Scale

PHQ Patient Health Questionnaire

PHQ-15 Patient Health Questionnaire 15

PHQ-2 short form of the Patient Health Questionnaire 9

PHQ-4 Patient Health Questionnaire 4

PHQ-9 Patient Health Questionnaire 9

PRIME-MD Primary Care Evaluation of Mental Disorders

RCD/TMD Research Diagnostic Criteria for Temporomandibular Disorders

SDATA Survey Data

SBL Schmerzbeschreibungsliste

SSC Somatosensory symptom checklist

THI-12 Tinnitus Handicap Inventory 12

TMD Temporomandibular disorder

UZH University of Zurich

WISE web-based interdisciplinary symptom evaluation

9. Ethics approval and consent to participate

Not applicable

10. Consent for publication

Not applicable

11. Availability of data and materials

Following we provide a link that enables readers to fill in an exemplary questionnaire which will result in the automatic creation of a single case summary report:

http://www.scientific-affairs.ch/limesurvey/index.php/877782?lang=en

The single case summary report was developed with JavaScript and JQuery, the scripts for retrieving data from the database in PHP.

The WISE was conceptualized as a platform independent web-based tool. It has successfully been tested on the following operating systems and web-browsers:

Windows 10 Pro 64 bit
Google Chrome 48.0.2564.116 m
Microsoft Edge 25.10586.0.0
Mozilla Firefox 43.0.4

Windows 7 Home Premium 64 bit
Google Chrome Version 51.0.2704.103 m
Mozilla Firefox Version 47.0

OS X El Capitan (10.11.6)
Safari Version 9.1.2 (11601.7.7)
Mozilla Firefox Version 39.0

Linux Mint 17.3 Cinnamon 64 bit
Google Chrome Version 51.0.2704.79
Mozilla Firefox 43.0

Android 4.2.2
Google Chrome 51.0.2704.81
Mozilla Firefox 48.0

12. Competing interests

None of the authors declare any conflict of interest.

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14. Authors' contributions

Dominik A. Ettlin	conception and design, drafting of the manuscript, and intellectual contributions to the content
Isabelle Sommer	intellectual contributions to the content
Ben Brönnimann	intellectual contributions to the content
Jörg Scheidt	intellectual contributions to the content
Sergio Maffioletti	conception and design of the section “data security and storage”, technical setup of the UZH-Server
Mei-Yin Hou	intellectual contributions to the content
Nenad Lukic	intellectual contributions to the content
Beat Steiger	conception and design, drafting of the manuscript, and intellectual contributions to the content, technical implementation of the WISE with LimeSurvey, technical implementation of the single case summary report

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16. References

1. Lazaridou A, Edwards RR (2016) Getting personal. Pain 157(1): 1–2. doi: 10.1097/j.pain.0000000000000376

2. Dworkin SF, LeResche L (1992) Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 6(4): 301–355

3. Schiffman E, Ohrbach R, Truelove E et al. (2014) Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†. J Oral Facial Pain Headache 28(1): 6–27. doi: 10.11607/jop.1151.

4. Garofalo JP, Gatchel RJ, Wesley AL et al. (1998) Predicting chronicity in acute temporomandibular joint disorders using the research diagnostic criteria. J Am Dent Assoc 129(4): 438–447

5. Dworkin SF, Sherman J, Mancl L et al. (2002) Reliability, validity, and clinical utility of the research diagnostic criteria for Temporomandibular Disorders Axis II Scales: depression, non-specific physical symptoms, and graded chronic pain. J Orofac Pain 16(3): 207–220

6. Dougall AL, Jimenez CA, Haggard RA et al. (2012) Biopsychosocial factors associated with the subcategories of acute temporomandibular joint disorders. J Orofac Pain 26(1): 7

7. Sharpe L (2016) Psychosocial management of chronic pain in patients with rheumatoid arthritis: challenges and solutions. J Pain Res 9: 137

8. M Adams L, C Turk D (2015) Psychosocial factors and central sensitivity syndromes. Curr Rheumatol Rev 11(2): 96–108

9. Burns L, Ritvo S, Ferguson M et al. (2015) Pain catastrophizing as a risk factor for chronic pain after total knee arthroplasty: a systematic review. J Pain Res 8: 21–32

10. Kirkpatrick BE, Riggs ER, Azzariti DR et al. (2015) GenomeConnect: Matchmaking Between Patients, Clinical Laboratories, and Researchers to Improve Genomic Knowledge. Hum Mutat 36(10): 974–978

11. Wang RT, CA SF, Ulm JW et al. (2013) Online self-report data for duchenne muscular dystrophy confirms natural history and can be used to assess for therapeutic benefits. PLoS currents 6

12. Ganser AL, Raymond SA, Pearson JD (2010) Data quality and power in clinical trials: a comparison of ePRO and paper in a randomized trial. In: Byrom B, Tiplady B (eds) ePro: Electronic solutions for patient-reported data. Gower, Farnham, Surrey, England, pp 49–78

13. Institute of Medicine (U.S.) (2001) Crossing the quality chasm: A new health system for the 21st century. National Academy Press, Washington, D.C.

14. Snyder CF, Jensen RE, Segal JB et al. (2013) Patient-reported outcomes (PROs): putting the patient perspective in patient-centered outcomes research. Med Care 51(8 Suppl 3): S73-9. doi: 10.1097/MLR.0b013e31829b1d84

15. Centers for Medicare & Medicaid Services, CMS (2016AM) Electronic Health Records (EHR) Incentive Programs

16. Campbell N, Ali F, Finlay AY et al. (2015) Equivalence of electronic and paper-based patient-reported outcome measures. Quality of Life Research 24(8): 1949–1961

17. Coons SJ, Eremenco S, Lundy JJ et al. (2014) Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. Patient. doi: 10.1007/s40271-014-0090-z

18. Cella D, Gershon R, Lai J et al. (2007) The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. Qual Life Res 16 Suppl 1: 133–141. doi: 10.1007/s11136-007-9204-6

19. Stanford Medicine Systems Neuroscience and Pain Lab (2015) Collaborative Health Outcome Information Registry (CHOIR). http://snapl.stanford.edu/choir/

20. LimeSurvey Project Team / Carsten Schmitz (2015) LimeSurvey: An Open Source survey tool. www.limesurvey.org

21. Treworgy J ImageMapster. http://www.outsharked.com/imagemapster/

22. Petersen S, Schroijen M, Molders C et al. (2014) Categorical interoception: perceptual organization of sensations from inside. Psychol Sci 25(5): 1059–1066. doi: 10.1177/0956797613519110

23. Carleton RN, Duranceau S, Freeston MH et al. (2014) "But it might be a heart attack": intolerance of uncertainty and panic disorder symptoms. J Anxiety Disord 28(5): 463–470. doi: 10.1016/j.janxdis.2014.04.006

24. International RDC/TMD Consortium Network DC/TMD Symptom Questionnaire. http://www.rdc-tmdinternational.org/Portals/18/protocol_DC-TMD/DC-TMD_SQ_short-form_2013-05-12.pdf?ver=2014-02-04-113445-207

25. Kroenke K, Spitzer RL, Williams, Janet B W (2002) The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 64(2): 258–266

26. Spitzer RL, Williams JB, Kroenke K et al. (2000) Validity and utility of the PRIME-MD Patient Health Questionnaire in assessment of 3000 obstetric-gynecologic patients: The PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. Am J Obstet Gynecol 183(3): 759–769. doi: 10.1067/mob.2000.106580

27. Löwe B, Wahl I, Rose M et al. (2010) A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. J Affect Disord 122(1-2): 86–95. doi: 10.1016/j.jad.2009.06.019

28. Kroenke K, Spitzer RL, Williams JBW et al. (2009) An ultra-brief screening scale for anxiety and depression: the PHQ-4. Psychosomatics 50(6): 613–621. doi: 10.1176/appi.psy.50.6.613

29. Khubchandani J, Brey R, Kotecki J et al. (2016) The Psychometric Properties of PHQ-4 Depression and Anxiety Screening Scale Among College Students. Arch Psychiatr Nurs 30(4): 457–462. doi: 10.1016/j.apnu.2016.01.014

30. Löwe B, Decker O, Müller S et al. (2008) Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 46(3): 266–274. doi: 10.1097/MLR.0b013e318160d093

31. Narayana A, Katz N, Shillington AC et al. (2015) National Breakthrough Pain Study: prevalence, characteristics, and associations with health outcomes. Pain 156(2): 252–259

32. Kroenke K, Spitzer RL, Williams JBW et al. (2010) The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry 32(4): 345–359. doi: 10.1016/j.genhosppsych.2010.03.006

33. Spitzer RL, Kroenke K, Williams JBW et al. (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166(10): 1092–1097. doi: 10.1001/archinte.166.10.1092

34. Kroenke K, Spitzer RL, Williams JB (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16(9): 606–613

35. Kujanpää T, Ylisaukko-Oja T, Jokelainen J et al. (2014) Prevalence of anxiety disorders among Finnish primary care high utilizers and validation of Finnish translation of GAD-7 and GAD-2 screening tools. Scand J Prim Health Care 32(2): 78–83

36. Spitzer RL, Kroenke K, Williams JBW et al. (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166(10): 1092–1097

37. Korff M von, Ormel J, Keefe FJ et al. (1992) Grading the severity of chronic pain. Pain 50(2): 133–149

38. Türp JC, Jokstad A, Motschall E et al. (2007) Is there a superiority of multimodal as opposed to simple therapy in patients with temporomandibular disorders? A qualitative systematic review of the literature. Clin Oral Implants Res 18 Suppl 3: 138–150. doi: 10.1111/j.1600-0501.2007.01480.x

39. Sullivan, Michael J. L., Bishop SR, Pivik J (1995) The Pain Catastrophizing Scale: Development and validation. Psychol Assess 7(4): 524–532. doi: 10.1037/1040-3590.7.4.524

40. Alsaadi SM, McAuley JH, Hush JM et al. (2013) Detecting insomnia in patients with low back pain: accuracy of four self-report sleep measures. BMC Musculoskelet Disord 14(1): 1

41. Savard M, Savard J, Simard S et al. (2005) Empirical validation of the Insomnia Severity Index in cancer patients. Psycho-Oncology 14(6): 429–441

42. Smith S, Trinder J (2001) Detecting insomnia: comparison of four self-report measures of sleep in a young adult population. J Sleep Res 10(3): 229–235

43. Bastien CH, Vallières A, Morin CM (2001) Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2(4): 297–307

44. Broadbent E, Petrie KJ, Main J et al. (2006) The brief illness perception questionnaire. J Psychosom Res 60(6): 631–637. doi: 10.1016/j.jpsychores.2005.10.020

45. Galli U, Ettlin DA, Palla S et al. (2010) Do illness perceptions predict pain-related disability and mood in chronic orofacial pain patients? A 6-month follow-up study. Eur J Pain 14(5): 550–558. doi: 10.1016/j.ejpain.2009.08.011

46. Sullivan, Michael J L, Adams H, Horan S et al. (2008) The role of perceived injustice in the experience of chronic pain and disability: scale development and validation. J Occup Rehabil 18(3): 249–261. doi: 10.1007/s10926-008-9140-5

47. Mancuso SG, Knoesen NP, Castle DJ (2010) The Dysmorphic Concern Questionnaire: A screening measure for body dysmorphic disorder. Aust N Z J Psychiatry 44(6): 535–542. doi: 10.3109/00048671003596055

48. Oosthuizen P, Lambert T, Castle DJ (1998) Dysmorphic concern: prevalence and associations with clinical variables. Aust N Z J Psychiatry 32(1): 129–132

49. International RDC/TMD Consortium Network Jaw Function Questionnaire. http://www.rdc-tmdinternational.org/Portals/18/protocol_RDC/Jaw%20Function%20Questionnaire.pdf

50. Wolford LM, Mercuri LG, Schneiderman ED et al. (2015) Twenty-year follow-up study on a patient-fitted temporomandibular joint prosthesis: the techmedica/TMJ concepts device. J Oral Maxillofac Surg 73(5): 952–960

51. Bankstahl US, Elkin EP, Gebauer A et al. (2012) Validation of the THI-12 questionnaire for international use in assessing tinnitus: a multi-centre, prospective, observational study. International J Audiol 51(9): 671–677

52. Ertaş M, Baykan B, Tuncel D et al. (2009) A comparative ID migraine screener study in ophthalmology, ENT and neurology out-patient clinics. Cephalalgia 29(1): 68–75. doi: 10.1111/j.1468-2982.2008.01702.x

53. Lipton RB, Dodick D, Sadovsky R et al. (2003) A self-administered screener for migraine in primary care: The ID Migraine validation study. Neurology 61(3): 375–382

54. Phillips C, Essick G, Blakey G et al. (2007) Relationship between patients' perceptions of postsurgical sequelae and altered sensations after bilateral sagittal split osteotomy. J Oral Maxillofac Surg 65(4): 597–607

55. Fillingim RB, Ohrbach R, Greenspan JD et al. (2011) Potential psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain 12(11 Suppl): T46-60. doi: 10.1016/j.jpain.2011.08.007

56. Cook KF, Dunn W, Griffith JW et al. (2013) Pain assessment using the NIH Toolbox. Neurology 80(11 Supplement 3): S49-S53. doi: 10.1212/WNL.0b013e3182872e80

57. Pfingsten M, Nagel B, Emrich O et al. (2012) Deutscher Schmerzfragebogen: Handbuch v.2012.2

58. Steiger B, Ettlin D (2015) Besonderheiten der orofazialen Schmerzempfindung (Distinctive features of orofacial pain perception). Schmerz 29(2): 163–170. doi: 10.1007/s00482-015-1516-9

59. Treede R, Rief W, Barke A et al. (2015) A classification of chronic pain for ICD-11. Pain 156(6): 1003–1007. doi: 10.1097/j.pain.0000000000000160

60. PEABODY FW (1927) The care of the patient. JAMA 88(12): 877. doi: 10.1001/jama.1927.02680380001001

61. Durham J, Raphael KG, Benoliel R et al. (2015) Perspectives on next steps in classification of oro-facial pain - part 2: Role of psychosocial factors. J Oral Rehabil 42(12): 942–955. doi: 10.1111/joor.12329

62. Loeser J (2000) Pain and suffering. Clin J Pain(16 (2 Suppl)): 2–6

63. WEISS DJ, KINGSBURY GG (1984) Application of computerized adaptive testing to educational problems. J Educ Meas 21(4): 361–375. doi: 10.1111/j.1745-3984.1984.tb01040.x

64. Klasser GD, Gremillion HA (2013) Past, present, and future of predoctoral dental education in orofacial pain and TMDs: a call for interprofessional education. J Dent Educ 77(4): 395–400

65. Jones RV (1986) Working together-learning together. Occas Pap R Coll Gen Pract(33): 1

66. Institute of Medicine . Committee on Planning a Continuing Health Care Professional Education Institute (2010) Redesigning continuing education in the health professions. National Academies Press, Washington, D.C.

67. Ritenbaugh C, Hammerschlag R, Dworkin SF et al. (2012) Comparative effectiveness of traditional chinese medicine and psychosocial care in the treatment of temporomandibular disorders-associated chronic facial pain. J Pain 13(11): 1075–1089

68. Bair E, Brownstein NC, Ohrbach R et al. (2013) Study protocol, sample characteristics, and loss to follow-up: The OPPERA prospective cohort study. J Pain 14(12): T2-T19

69. Herman PM, Dodds SE, Logue MD et al. (2014) IMPACT-Integrative Medicine PrimAry Care Trial: protocol for a comparative effectiveness study of the clinical and cost outcomes of an integrative primary care clinic model. BMC Complement Altern Med 14(1): 132

70. Dworkin RH, McDermott MP, Farrar JT et al. (2014) Interpreting patient treatment response in analgesic clinical trials: Implications for genotyping, phenotyping, and personalized pain treatment. Pain 155(3): 457–460

71. Lazaridou A, Edwards RR (2016) Getting personal: the role of individual patient preferences and characteristics in shaping pain treatment outcomes. Pain 157(1): 1–2

72. Nixdorf, Drangsholt MT, Ettlin DA et al. (2012) Classifying orofacial pains: a new proposal of taxonomy based on ontology. J Oral Rehabil 39(3): 161–169

73. Robinson PN, Mundlos S (2010) The human phenotype ontology. Clinical genetics 77(6): 525–534

74. Ceusters W, Michelotti A, Raphael KG et al. (2015) Perspectives on next steps in classification of oro-facial pain-part 1: role of ontology. J Oral Rehabil 42(12): 926–941

75. Ceusters W, Smith B (2010) Foundations for a realist ontology of mental disease. J Biomed Semantics 1(10): 1–10

76. Jensen M, Cox AP, Chaudhry N et al. (2013) The neurological disease ontology. J Biomed Semantics 4(1): 1

77. Garcia-Campayo J, Zamorano E, Ruiz MA et al. (2010) Cultural adaptation into Spanish of the generalized anxiety disorder-7 (GAD-7) scale as a screening tool. Health Qual Life Outcomes 8(1): 8. doi: 10.1186/1477-7525-8-8

78. Donker T, van Straten A, Marks I et al. (2011) Quick and easy self-rating of Generalized Anxiety Disorder: validity of the Dutch web-based GAD-7, GAD-2 and GAD-SI. Psychiatry Res 188(1): 58–64

79. Seo J, Park S (2015) Validation of the Generalized Anxiety Disorder-7 (GAD-7) and GAD-2 in patients with migraine. J Headache Pain 16(1): 1–7

Table 1: Publicly available questionnaires used in the construction of the WISE for OFP and TMD.

Domain	Questionnaire (Abbreviation)	Type of scales, number of items	Range per item	Maximum score Possible cut-off values for further evaluation
Stress	Patient Health Questionnaire Stress (PHQ-S)[26]	ordinal 10	0-2	20 10-14: moderate >14: severe
Anxiety	General Anxiety Questionnaire 7 (GAD-7)[36]	ordinal 7	0-3	21 7-12[35, 36, 77–79]
Depression	Patient Health Questionnaire 9 (PHQ-9)[34]	ordinal 9	0-3	27 8-11[35, 36]
Pain related disability	Graded Chronic Pain Scale (for orofacial pain / body pain) (GCPS) [37]	numeric 7	0-10	6 3[37]
Pain catastrophizing	Pain Catastrophizing Scale (PCS)[39]	ordinal 4	0-4	52 30[39]
Illness perception	Brief Illness Perception Questionnaire (B-IPQ)[44]	numeric 8	0-10	80 n/a
Injustice experience	Injustice Experience Questionnaire (IEQ) [46]	ordinal 12	0-4	48 30[46]
Dysmorphic concern	Dysmorphic concern questionnaire (DCQ) [47]	ordinal 7	0-3	21 9[47]
TMD Symptoms	DC-TMD Symptom Checklist[24] (DC-TMD-SQ)	Checklist 14	0-1	n/a

Jaw function	Modified Jaw Function Questionnaire (JFQ)[49, 50]	Checklist 10 nominal 2	0-1 0-10	n/a n/a
Tinnitus	Tinnitus Handicap Inventory 12 (THI-12)[51]	ordinal 12	0-2	24 10[51]
Headache	ID-migraine screener[53]	Checklist 3	0-1	3 2[53]
Sleep	Insomnia Severity Index (ISI)[43]	ordinal 7	0-4	28 14[40–42]
Somatosensory dysfunction	Somatosensory Symptom Checklist (SSC)[54]	Checklist	0-7	n/a

Table 2: WISE items and checklist content sources, case-finding tools and other symptom exploration instruments.

Symptom domain	Checklist item	Source	Threshold	In-depth assessment
head and orofacial area	1) Toothache / oral pain (e.g., tongue, gums)	none		
	2) Pain / tightness in the jaw or face	DC-TMD-SQ:1		
	3) Ear pain, ear pressure, tinnitus (e.g., ringing noise)	DC-TMD-SQ:1	a little	THI-12
	4) Headache	DC-TMD-SQ:2	a little	ID-Migraine Screener
	Σ(1..4)		1	PAIN-head/face GCPS- head/face
	5) Limitation/pain upon mouth opening or closing (e.g. yawning)	DC-TMD-SQ: 9&13	a lot	modified JFQ
	6) Limitation/pain upon biting/chewing/talking/drinking	DC-TMD-SQ: 4&7	a lot	modified JFQ
	7) Temporomandibular joint (TMJ) noises (e.g., clicking, crepitus)	DC-TMD-SQ:8	a little	clicking crepitus other
	8) Tooth / jaw position (e.g., bite is incorrect) / physical appearance	none	a lot	DCQ
	9) Abnormal sensations in the mouth, lips or face that have negative effects (e.g., uncontrolled drooling)	SSC	a lot	SSC, modified JFQ
	10) Dry mouth/malodor/swallowing difficulties	none		
other pain	11) Pain in the neck/shoulder	none		
	12) Pain in the back area	PHQ-15:2		
	13) Pain in the chest/abdomen/genitals	PHQ-15:1,4,6 & 11	a little	PAIN-torso
	14) Pain in the arms, legs	PHQ-15:3		
	Σ(11,12,14)		1	GCPS-B

				PAIN-body
other symptoms	15) Worries about my chief complaint(s)	PHQ-S:1	a lot	B-IPQ, PCS
	16) Increased fatigue/loss of energy/unintentional weight loss or gain	PHQ-15:14	a lot	PHQ-9
	17) Snoring/apnea during sleep	none		
	18) Dizziness/nausea/fainting spells/shortness of breath/feeling your heart pound or race/indigestion	PHQ-15:7-10,13	a lot	PHQ-S
	19) Lack of time/work related stress/caring responsibilities/finances	PHQ-S:5-7	a lot	PHQ-S
	20) Lack of support/interpersonal conflicts/loneliness	PHQ-S:4,8	a lot	PHQ-S
	21) Different opinions of different caregivers/not been taken seriously	none	a lot	IEQ
	22) Stressful life events (something bad that happened recently or in the past with corresponding thoughts/ dreams/feelings)	PHQ-S:9,10	a lot	PHQ-S

Table 3. PHQ-4 screening items and thresholds for related case-finding tools. A value of >2 (yellow flag) was chosen for a further evaluation by GAD-7 and by PHQ-9. For item 27, a value of > 1 was used as threshold for presenting the ISI.

Checklist item (continued)	**Source**	**Threshold**	In-depth assessment
23) Feeling nervous, anxious or on edge	GAD-2	Σ > 2	GAD-7
24) Not being able to stop or control worrying			
25) Little interest or pleasure in doing things	PHQ-2	Σ > 2	PHQ-9
26) Feeling down, depressed, or hopeless			
27) Trouble falling or staying asleep, or sleeping too much	PHQ-9	> 1	ISI

Table 4: Checklist items capturing aspects of injustice experience and being a burden to others.

Checklist item (continued)	source	**threshold**	In-depth assessment
28) Did you experience injustice concerning your chief complaints (e.g., misinformation, mistreatment, undue expense etc.)?	none	yes	IEQ
29) Are you concerned about being a burden to others?	none	yes	B-IPQ

2.2 *Empirical study 2*

Novel Air Stimulation MR-Device for Intraoral Quantitative Sensory Cold Testing

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The advent of neuroimaging in dental research provides exciting opportunities for relating excitation of trigeminal neurons to human somatosensory perceptions. Cold air sensitivity is one of the most frequent causes of dental discomfort or pain. Up to date, devices capable of delivering controlled cold air in an MR-environment are unavailable for quantitative sensory testing. This study therefore aimed at constructing and evaluating a novel MR-compatible, computer-controlled cold air stimulation apparatus (CASA) that produces graded air puffs. CASA consisted of a multi-injector air jet delivery system (AJS), a cold exchanger, a cooling agent, and a stimulus application construction. Its feasibility was tested by performing an fMRI stimulation experiment on a single subject experiencing dentine cold sensitivity. The novel device delivered repetitive, stable air stimuli ranging from room temperature (24.5°C ± 2°C) to −35°C, at flow rates between 5 and 17 liters per minute (l/min). These cold air puffs evoked perceptions similar to natural stimuli. Single-subject fMRI-analysis yielded brain activations typically associated with acute pain processing including thalamus, insular and cingulate cortices, somatosensory, cerebellar, and frontal brain regions. Thus, the novel CASA allowed for controlled, repetitive quantitative sensory testing by using air stimuli at graded temperatures (room temperature down to −35°C) while simultaneously recording brain responses. No MR-compatible stimulation device currently exists that is capable of providing non-contact natural-like stimuli at a wide temperature range to tissues in spatially restricted areas such as the mouth. The physical characteristics of this novel device thus holds promise for advancing the field of trigeminal and spinal somatosensory research, namely with respect to comparing therapeutic interventions for dentine hypersensitivity.

Keywords: cold air stimulation, QST, fMRI, dentine hypersensitivity

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INTRODUCTION

Temperature perception and discrimination are part of the body's homeostatic control system that evaluates and integrates internal and external body states. At the cellular level, primary sensory afferents (C- and Aδ-fibers) possess thermoreceptors that transduce distinct temperature stimuli (McKemy, 2007). Innocuous cold perception (cryesthesia; 15 to –30˚C)is evoked by distinct nerve fibers that can be categorized as cold thermoreceptors whereas temperature stimuli below 15 °C are encoded by cold nociceptors. Peripheral cold temperature receptors belong to the transient receptor potential channel family (e.g., TRPM8 and TRPA1). Furthermore, sodium channels Nav1.8 and transient 4-AP-sensitive K+ currents are also involved in cold related cellular activation and inhibition (McKemy, 2013). Some of these ion channels have also been detected in dental tissue (Story et al., 2003; Patapoutian et al., 2009; Chung et al., 2013). In spite of the diversity of neural substrates for cold signaling, converging evidence suggests that the prime molecular detector of cold is TRPM8, a calcium-permeable cationic ion channel (Madrid and Pertusa, 2013). Both, mammalian dental pulp C- and Aδ-fibers express TRPM8 (Takashima et al., 2007). In molars of transgenic mice, a portion of TRPM8 labeled axons were observed below the odontoblast layers and more interestingly, another subset of TRPM8 fibers crossed the odondoblast layer to extend into dentinal tubules. This observation, taken with functional recordings in animals and psychophysical data in humans suggest that direct stimulation of TRPM8 neurons may play a more important role in dentine cold hypersensitivity than the more popular "hydrodynamic theory." The latter postulates that dentinal fluid movements evoke neural signaling (Chidchuangchai et al., 2007). By presenting a microscale model of tooth physiology, Lin M. et al. (2014) presented a synthesis of possible thermal transduction mechanisms in teeth from an engineering perspective, highlighting the activation of stress-sensitive ion channels on nociceptors by cooling effects.
On the brainstem level, unmyelinated, and small myelinated TRPM8 neurons from intra- and perioral areas predominantly project onto second order neurons in the rostral trigeminal sensory nuclei (Kim et al., 2014). Likely due to lack of cold stimulation techniques applicable in a magnetic resonance scanner environment, it remains an open question which areas of the human brain are involved in the processing of dentine cold hypersensitivity (Meier et al., 2012).
In the clinical environment, investigations on dentine hypersensitivity (DH) rely on a variety of qualitative or semi- quantitative dental stimulation techniques. These methods encompass

Yeaple®R pressure probes (Chabanski et al., 1997), percussion testing, bite stress tests, water syringe, and piezoelectric magnetomechanical devices for applying vibrotactile stimuli to teeth. Other approaches include air application from triple air syringes or cold sprays at freezing temperatures. Cool or warm spatula have also been used for sensory testing. Non-contact air puff stimulators comprising pneumatically and mechanically driven devices are mainly used in research settings (Puce et al., 1995; Wallois et al., 1997; Keller et al., 2002; Briggs et al., 2004; Ettlin et al., 2004; Moana-Filho et al., 2010; Pigg et al., 2010; Lindstedt et al., 2011; Svensson et al., 2011; Ahn et al., 2012; Brügger et al., 2012; Meier et al., 2012).
Current experimental thermal stimulation tools are limited in their ability to produce computer-controlled, graded, non- contact and cold temperature stimuli for quantitative sensory testing (QST) and none is applicable in a high magnetic field environment such as an MR-scanner. For extraoral air stimulation Servos et al. (1998) used an MR-compatible air stimulation device capable of applying very short air puffs on the skin at room temperature. Using the same temperature range, Meier et al. (2012) used an MR-compatible air stimulation device for investigating DH subjects' brain responses.
Arguably, cold temperature stimuli most closely imitate naturally occurring DH. Therefore, the aim of this study was (1) to design and construct a novel MR-compatible and computer- controlled dental stimulation device capable to operate in a broad range of cold temperatures, and (2) to show its MR-feasibility in a single DH subject.
MATERIALS AND METHODS

The experiment was previously approved by the local ethics committee (KEK-ZH-Nr. 2010-0347) and the volunteer signed an informed consent.

System Design

The cold air stimulation apparatus (CASA) was designed to include four tube-connected components (Figure 1): (1) An air source that does not condense at very low temperatures and that feeds into a computer-controlled air jet delivery system, (2) a cold exchange system (CE), and (3) an air switch that directs the cold stimulus to and away from the target tooth. A temperature sensor served for monitoring stimulation temperature.

Instead of regular air, compressed nitrogen of high purity was used in order to prevent tube condensation and freezing upon gas cooling.

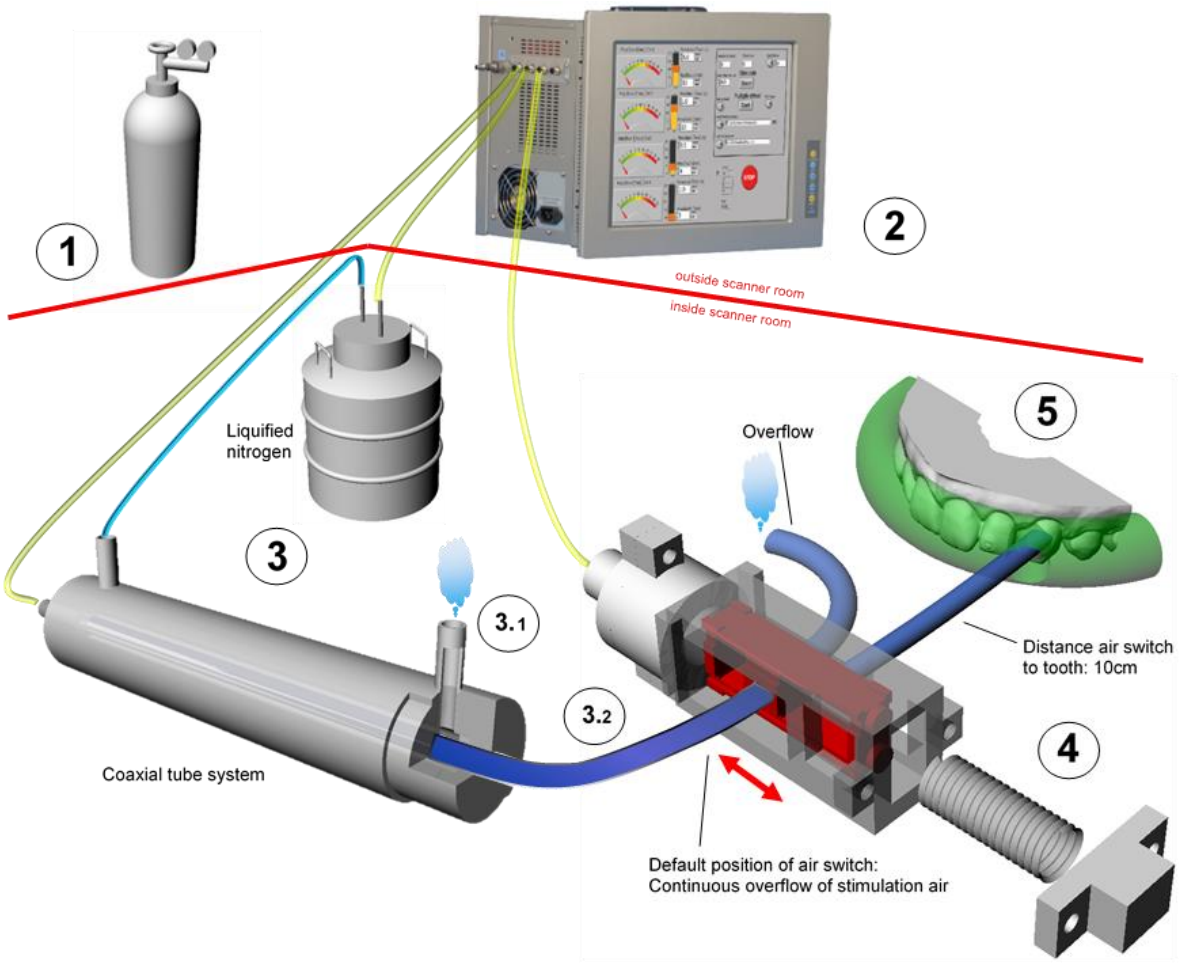

Fig. 1: Schematic display of the CASA components (graphical objects not shown in proportional scale). Outside scanner room: (1) Air source (2) Computer-controlled air jet delivery system with three outlets: cooling system, stimulation air, and pneumatic control of air switch. Inside scanner room: (3) Cold exchanger [note: the two gas circuits for cooling (3.1) and stimulation (3.2) are completely separated] (4) Air switch composed of mobile slider (in red) and spring (5) Only one target tooth is exposed to air while the others are shielded by impression material (transparent green). The various colors of the connecting tubes reflect different air temperatures (T°) in the tubes: room T° (yellow); approx. −196°C (light blue); target T° for tooth stimulation (dark blue).

Air Jet Delivery System

A modified version of the previously developed multi-injector AJS was used that consists of four computer-controlled channels of which three were used for the CASA (Megias-Alguacil et al., 2008). This system is able to apply air flow rates between 0.3 and 20 l/min in steps of 0.1 l/min. One channel delivered nitrogen steam from a cryotank to the CE (see Section Cold Exchange System and Temperature Regulation, Figure 1). A second channel served to deliver temperature-graded air puffs to the target tooth. A third channel controlled the position of

the air switch delivering the stimulus to the target tooth (see Section Air Switch and Dental Splint).

Cold Exchange System and Temperature Regulation

The stimulation air was cooled by the CE which consisted of a 1.75 m long coaxial tube system made of non-ferromagnetic pure stainless steel (Inox-steel-technology, Edelstahl-Anlagebau, CH-3645 Thun, Switzerland). Its outer chamber had two outlets for circulatory flow of nitrogen steam (−196°C) delivered by a liquid nitrogen tank (Figure 1). The temperature of the stimulation air passing through the inner chamber was controlled by adapting the flow rate of the nitrogen steam in the outer chamber by the AJS. To avoid subject contact, the tube releasing the outflowing nitrogen steam was positioned away from the subject. All tube connections were made of cryoresistant Polytetrafluorethylen (PTFE) and had an inner diameter of 4 mm (Maagtechnic AG, CH-8600 Duebendorf, Switzerland). MR-compatible pure stainless steel connections served as tube connectors (Swagelock®, Arbor AG, CH-5443 Niederrohrdorf). Highly flexible elastomeric material was used for maximum thermal tube insulation (Armaflex®, Regisol AG, CH-3292 Busswil). For monitoring stimulation air temperature and humidity, a fiberoptic temperature sensor (Reflex® 4 channel, Neoptix®, Canada) and a humidity sensor (SHT1x, Sensirion®, CH-8712 Staefa) were positioned after the air switch.

Air Switch and Dental Splint

Due to the air's low thermal capacity, turning off the flow of cold air would result in its immediate and uncontrolled warming. To avoid this scenario, we opted for a continuous stimulation air flow. For on-and-off tooth stimulation, a custom made MR-compatible air switch was built (Fig. 1) by means of 3D design software (Rhino 5.0®) and subsequent printing on a 3D printer using Rigid Opaque Gray Material (Objet Eden 260V®, Stratasys, Eden Prairie, MN, 55344 USA). The time lag of the slider position change to the target tissue was estimated using the formula:

$$\Delta t = \frac{V}{\hat{V}} = \frac{A^{*}L}{\hat{V}}$$

where Δt is the lag from switch operation to tooth stimulation, V the stimulation air tube's volume (length 0.1 m, diameter 2 mm), ^V the volume flow (13 l/min.), A the tube's cross section area and L the tube's length (0.1 m).

The air switch was attached to the MR head coil by plastic cable ties. In non-stimulation mode, the slider was held in position by a custom-designed non-ferromagnetic phosphor-bronze compression spring (Favre-Steudler SA, CH-2504 Biel- Bienne, Switzerland). For tooth stimulation, the spring force was counteracted by air pressure so that the cold air was directed toward the tooth (Figure 1).

To secure stimulation of one single target tooth, all other teeth were tightly covered by a subject tailored dental splint made of thixotropic vinyl polysiloxane (Blue mousse®R , Parkell, Inc., Edgewood, NY 11717 USA).

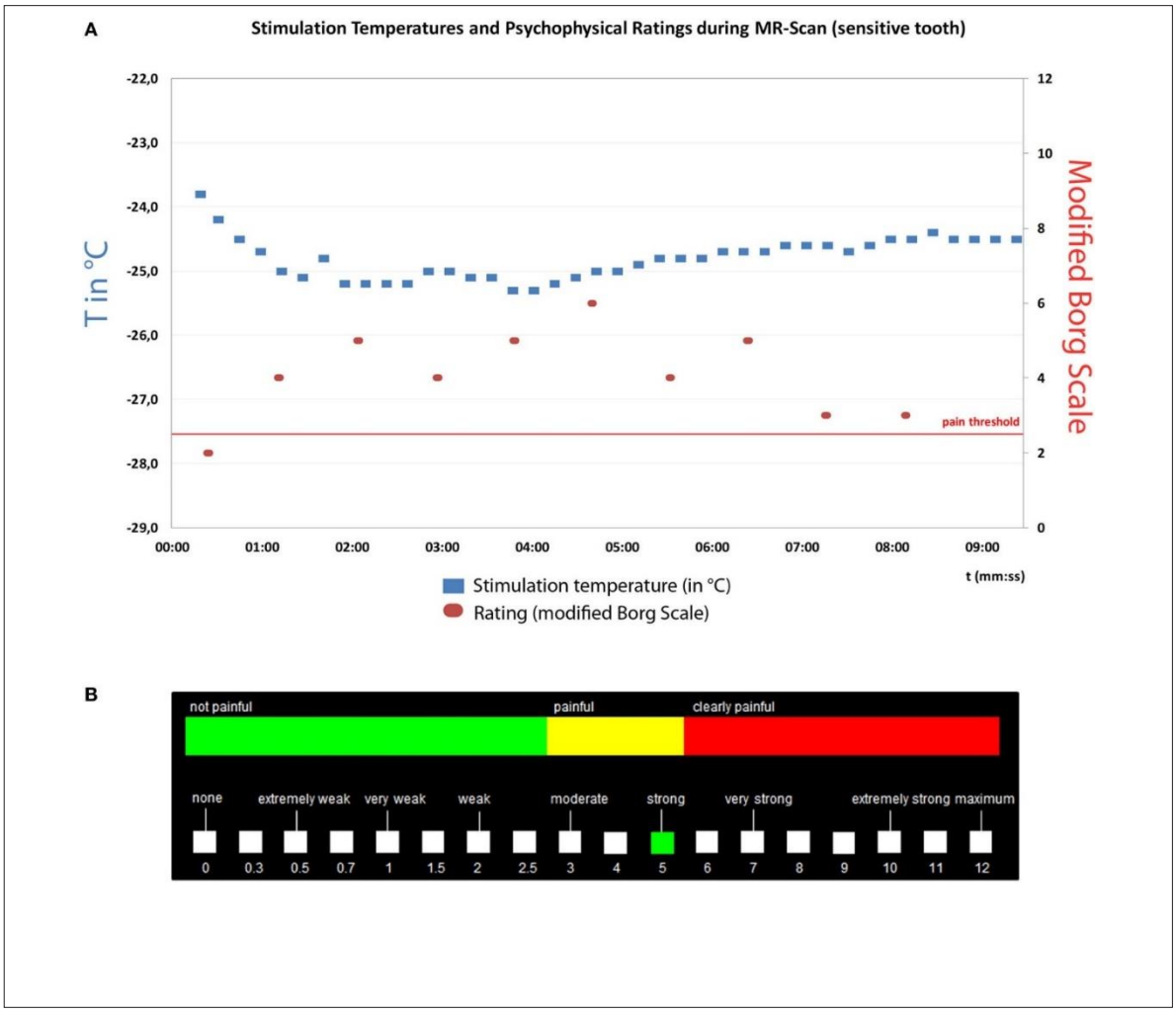

Fig. 2 : (A) Psychophysical testing of a sensitive tooth during MR scan in a single subject. Left x-axis: Stimulation temperature in °C (blue dots), Right y-axis: Subject ratings on modified BORG scale (red dots), x-axis: time (minutes). Pain threshold was defined as BORG score >2.5. (B) The BORG scale was presented on a screen and consisted of non-linearly distributed numerical (from 0 to 12), verbal (from none to maximum) and color-coded (green, non-painful; yellow, painful; red, clearly painful) descriptors of the sensory perception.

Monitoring of Target Tooth Temperature

A supplemental ex vivo cold air stimulation experiment was performed to assess cooling effects on the target tooth. For this purpose a temperature flow sensor was placed on the palatal surface while directing cold air of −35°C to the labial surface for 10 s (gSKIN® , GreenTEG, CH-8005 Zürich, Switzerland).

MR Feasibility Testing

To test the functioning of all system components and to explore supraspinal effects of the cold stimulus, an fMRI experiment was performed on a single DH subject (female, 25 years). For tooth screening, the sensitivity of the front teeth and premolars was qualitatively assessed by directing air to the teeth at room temperature (24.5°C ± 2°C) at a flow rate of 10 l/min. The most sensitive tooth was determined both by using an oral pain report and the Schiff scale for dentine hypersensitivity (Schiff et al., 2006). Next, QST was performed by using the CASA. The air temperature applied to the target tooth was adjusted in 2°C increments (±1°C) in order to identify its pain threshold by the ascending methods of limits (stimulus duration of 3 s). Every stimulus was rated on a modified version of the Borg Scale (Borg, 1998). This scale consisted of non- linearly distributed numerical (from 0 to 12), verbal (from none to maximum) and color-coded (green = non-painful, yellow = painful, red = clearly painful) descriptors of the sensory perception (Figure 2B). We aimed at identifying the temperature that evoked a clear but tolerable pain rated 6 on the modified
BORG scale. The subject's perception of the stimulus quality was assessed by both, a free subject report and by forced choice responses for descriptors presented by Beissner (Beissner et al., 2010).
During MR-scanning the subject was then exposed to 40 cold air stimuli (duration 3 s) at the predetermined target temperature applied to the sensitive tooth with an interstimulus interval of 10 s (Figure 2A). To monitor stable stimulus perception during the fMRI measurement, the subject was asked to rate every fourth stimulus on the modified Borg Scale presented on a screen (Figure 2B) by operating a trackball (fORP 932 response package, Cambridge research systems, Rochester, Kent, ME2 4BH, UK). During non-rated stimulation a green cross (4 × 4 cm) was presented in the middle of a black screen.

Scanning Parameters

All measurements were performed on a 3-T whole-body MRI system (Philips Ingenia, Best, the Netherlands). For functional scanning, a blood oxygen level dependent (BOLD) sensitive single-shot gradient echo planar imaging sequence was used to acquire 33 axial slices, covering the entire cerebrum and cerebellum, using a 32- channel head coil (dStream Head 32ch coil, Philips). Parameters: echo time 30 ms, flip angle = 75°, repetition time 2586 ms, slice thickness 4 mm, inter-slice gap = 0 mm, field of view 230 mm and matrix size in plane 128 × 128, resulting in a voxel size of 2.75 × 2.75 × 4 mm. Six dummy scans were first acquired and discarded to reach steady state magnetization.
In addition, 180 high-resolution T1 weighted axial slices (spoiled gradient echo) were acquired with TR = 20 ms, flip angle = 20°, voxel size = 0.98 × 0.98 × 1.02 mm, FOV = 22 cm, matrix = 224 × 187.

Image Preprocessing and Event Related Analysis

SPM12 (version 6470) running on MatLab 2015a (The MathWorks, Massachusetts, USA) was used for the brain activity analysis (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional EPI volumes of each subject were corrected for differences in head motion, spatially normalized according to the Montreal Neurological Institute (MNI) space and finally smoothed with a 8 mm full-width at half-maximum (FWHM) Gaussian kernel. To control for confounding head movement effects, individual movement parameters (translations in x, y, and z-direction, as well as rotations around x, y, and z axis) were implemented in the 1st level model as regressors of no interest. Excessive head motion was defined as a dislocation of more than once the in-plane voxel resolution (>2.75 mm). For removing the low frequency noise, a high-pass filter with a cut-off of 128 s was used. The Borg Scale rating trials were modeled as regressors of no interest to exclude brain activation related to motor activity, resulting in 30 trials of interest (noxious cold air stimulation). These trials were modeled as boxcar regressors and convolved with the standard canonical hemodynamic response function (HRF) as implemented in SPM12. For the 1st level analysis, the general linear model (GLM) was fitted by a design matrix
composed of the onsets and duration (3 s) of the noxious air stimuli.

Activations were considered as statistically significant when falling below a statistical threshold of $p < 0.05$, corrected for multiple comparisons using voxel-wise family-wise error correction (FWE). Finally, a T-contrast was computed to investigate whole-brain activity based on the contrast "noxious cold air stimulation vs. baseline (no stimulation)." Peak coordinates of the clusters were extracted and the respective anatomical locations were identified by means of the Automated Anatomical Labeling (AAL) atlas using the WFU pickatlas toolbox (http://fmri.wfubmc.edu/software/ pickatlas).

RESULTS

Stimulus Characteristics

Within the MR scanner, CASA allowed the intraoral application of air stimuli at temperatures ranging from room temperature to <–40°C at flow rates ranging from five to a maximum of 17 l/min. Minimal stimulation duration was 0.6 s, with a maximum of several minutes. The CE system allowed a manually controlled temperature adjustment within several minutes. Once the stimulus air temperature was reached, it could be kept constant with a tolerance of ±2°C for a maximum of 9 min (Figure 2).

Air Switch and Stimulation Tooth

The air switch could redirect a constant flow of cold air toward a target tooth at temperatures reaching <–40°C for a short time range (several seconds). For longer lasting stimulation periods a minimum of –35°C turned out to be appropriate to avoid freezing of the air switch. Flow rate measurements revealed an overall reduction of 0.3 l/min (SD 0.24 l/min) of the preset Air Jet output flow rate compared to the flow rate reaching the target tooth due to minor air loss within the air switch. The approximate air travel time from the switch valve to the target tooth lasted 222 ms. This value was calculated by adding up the 220 ms switch sliding time (mean of five measurements using a 10 m long non-curled silicone tube of 4 mm diameter and the air flow set to 13 l/min) with the 2 ms air column movement time (see formula in Section Air Switch and Dental Splint).

Temperature Flow Measurement on Tooth

By placing a temperature flow sensor (gSKIN®R , GreenTEG, CH-8005 Zürich) on the palatinal surface of an extracted tooth, temperature flow measurements during cold air stimulation applied to the labial surface revealed that the temperature gradient between the opposing tooth surfaces remained constant across a 10 s stimulation period at −25°C.

Behavioral Results and MR Feasibility Testing

Repeated psychophysical assessment of the sensitive tooth (tooth 12) revealed a target temperature of −25°C at a flow rate of 16 l/min with a stimulus duration of 3 s for achieving a moderately painful sensation. The stimulus quality was described by subjects as “stinging” and “icy” like “cold air in wintertime.” The perception was only felt in the target teeth and not in adjacent tissues. No tactile perception was reported by subjects. During scanning the tooth 12 was exposed to 40 stimuli at a temperature of −24.8 ± 0.3°C (Figure 2A). The mean rating of sensitive tooth stimulations on the modified Borg scale was 4.1 (SD 1.2, Figure 2A).

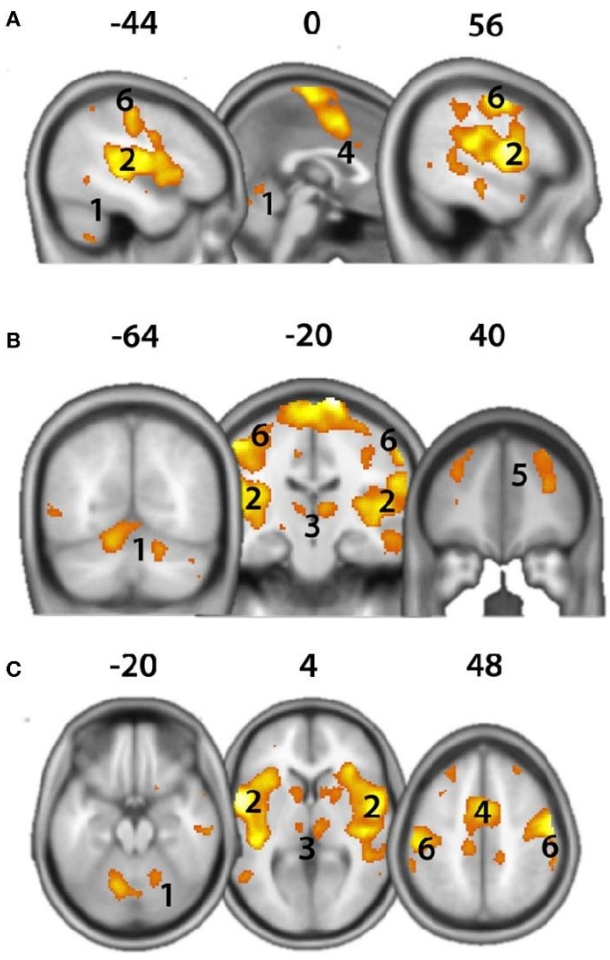

Fig. 3 : Brain activity evoked by noxious cold air stimulation (T-Contrast “Noxious cold air stimulation >no stimulation,” $p < 0.05$, FWE-corrected) evoked neural activity in wide regions of the brain. (A) Sagittal view; (B) coronal view; (C) axial view. 1, Cerebellum; 2, Insula; 3, Thalamus; 4, cingulate cortex; 5, Frontal cortex; 6, somatosensory cortex. X,Y,Z-coordinates are shown in MNI space.

fMRI Results

Head motion range was minimal (<1.8 mm). The brain activity analysis of noxious cold air stimulation revealed neural activity in an extensive network of brain regions. Significant brain activity could be observed in the cerebellum, in anterior-to-posterior portions of the insular cortex, in the primary and secondary

somatosensory cortex, in the thalamus, in cingulate cortices and in frontal regions (Figure 3, $p < 0.05$, FWE-corrected).

DISCUSSION

Since transduction mechanisms are determined by stimulus characteristics, QST of a specific stimulus type is an ideal method to assess sensory function and dysfunction. The main finding of this study demonstrated that the CASA is a useful tool for QST of sensitive teeth. It enables application of computer-controlled, intraoral and natural non-contact stimuli in the range of room temperature to −35°C in a 3 Tesla MR-environment. Further, it allowed recording of BOLD signals in response to painful intraoral cold air stimuli.

Principally, our fMRI paradigm can be modified for many research questions related to cold stimulus induced brain responses. In order to show the fMRI feasibility of our novel apparatus we chose a well-established fMRI paradigm based on model dependent and task-related brain activity. Using more sophisticated methods in future experiments such as model-free and/or time course analysis (Cauda et al., 2014) in combination with our novel apparatus will likely advance the understanding of trigeminal cold pain sensation. The current task related analysis of fMRI responses yielded brain activation typically associated with the "neuromatrix," a brain network that is involved in the processing of salient stimuli such as pain (Iannetti and Mouraux, 2010). Specifically, we observed significant neural responses in the thalamus, primary and secondary somatosensory cortices (Data Sheet 1), insular and cingulate cortices, frontal cortices and the cerebellum (Peyron et al., 2000; Apkarian et al., 2005; Iannetti and Mouraux, 2010; Moulton et al., 2010; Duerden and Albanese, 2013). Furthermore, current initial results show agreement with other reports focusing on brain activity of dental pain (Lin C. et al., 2014). Thus, the feasibility and MR-compatibility of the CASA have been confirmed.

Neuroscience aims at understanding nerve function along the entire neuraxis from stimulus transduction to central perception. Previous available experimental thermal stimulation tools were limited in their ability to apply reproducible computer- controlled, graded non-contact and cold temperature stimuli. None was applicable in a high magnetic field environment such as an MR-scanner. Natural cold air stimuli may best mimic clinically relevant pain experienced by DH patients. Furthermore, simultaneous recording of brain activity by means of fMRI might

broaden our knowledge of DH-related central processes. A first step in this direction was done by Meier et al. (2012) who stimulated sensitive teeth with air stimuli at room temperature within an MR environment. By comparison, our novel CASA opens up new possibilities by offering a broader stimulus temperature range up to freezing temperatures (<−35°C) thus providing more appropriate stimuli for investigating tooth sensitivity such as DH. Considering the complexity of peripheral signal transduction mechanisms, the application of graded non-contact cold stimuli might be helpful to further elucidate mechanisms of dental signal transduction (Lin M. et al., 2014). Finally, CASA can also be applied to other body parts and therefore allows novel opportunities for investigating supraspinal mechanisms of painless and painful cold perceptions.

Limitations

A limitation of the CASA is its time requirement for manual temperature calibration to reach the target temperature. It is shortened by progressively advanced operator experience. Future studies will have to demonstrate if the single-subject fMRI data observed in this report can be extrapolated to larger population groups.

AUTHOR CONTRIBUTIONS

BB: Development MR-compatible cold air stimulation device, recruitment, operation cold air stimulator during MR-measurement, statistical analysis. MM: MR- measurement, statistical analysis. MH: dental examination of subject. CP: Study design. DE: PI, Study design, development MR-compatible cold air stimulation device.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnhum. 2016.00335

REFERENCES

Ahn, D. K., Monbureau, O., Narhi, M., and Maixner, W. (2012). A novel computerized system for thermal stimulation of tooth in ferrets.
J. Neurosci. Methods 203, 305–310. doi: 10.1016/j.jneumeth.2011. 09.030

Apkarian, A. V., Bushnell, M. C., Treede, R., and Zubieta, J. (2005). Human brain mechanisms of pain perception and regulation in health and disease. Eur. J. Pain 9:463. doi: 10.1016/j.ejpain.2004.11.001

Beissner, F., Brandau, A., Henke, C., Felden, L., Baumgärtner, U., Treede, R., et al. (2010). Quick discrimination of A(delta) and C fiber mediated pain based on three verbal descriptors. PLoS ONE 5:e12944. doi: 10.1371/journal.pone.0012944

Borg, G. (1998). Borg's Perceived Exertion and Pain Scales. Champaign, IL: Human Kinetics.

Briggs, R. W., Dy-Liacco, I., Malcolm, M. P., Lee, H., Peck, K. K., Gopinath, K. S., et al. (2004). A pneumatic vibrotactile stimulation device for fMRI. Magn. Reson. Med. 51, 640–643. doi: 10.1002/mrm.10732

Brügger, M., Lutz, K., Brönnimann, B., Meier, M. L., Luechinger, R., Barlow, A., et al. (2012). Tracing toothache intensity in the brain. J. Dent. Res. 91, 156–160. doi: 10.1177/0022034511431253

Cauda, F., Costa, T., Diano, M., Sacco, K., Duca, S., Geminiani, G., et al. (2014). Massive modulation of brain areas after mechanical pain stimulation: a time-resolved FMRI study. Cereb. Cortex 24, 2991–3005. doi: 10.1093/cercor/ bht153

Chabanski, M. B., Gillam, D. G., Bulman, J. S., and Newman, H. N. (1997). Clinical evaluation of cervical dentine sensitivity in a population of patients referred to a specialist periodontology department: a pilot study. J. Oral Rehabil. 24, 666–672. doi: 10.1046/j.1365-2842.1997.00552.x

Chidchuangchai, W., Vongsavan, N., and Matthews, B. (2007). Sensory transduction mechanisms responsible for pain caused by cold stimulation of dentine in man. Arch. Oral Biol. 52, 154–160. doi: 10.1016/j.archoralbio.2006.09.009

Chung, G., Jung, S. J., and Oh, S. B. (2013). Cellular and molecular mechanisms of dental nociception. J. Dent. Res. 92, 948–955. doi: 10.1177/0022034513501877

Duerden, E. G., and Albanese, M. (2013). Localization of pain-related brain activation: a meta-analysis of neuroimaging data. Hum. Brain Mapp. 34, 109–149. doi: 10.1002/hbm.21416

Ettlin, D. A., Zhang, H., Lutz, K., Järmann, T., Meier, D., Gallo, L. M., et al. (2004). Cortical activation resulting from painless vibrotactile dental stimulation measured by functional magnetic resonance imaging (FMRI). J. Dent. Res. 83, 757–761. doi: 10.1177/154405910408301004

Iannetti, G. D., and Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). Exp. Brain Res. 205, 1–12. doi: 10.1007/s00221-010-2340-1

Keller, T., Popovic, M. R., Pappas, I. P. I., and Müller, P. (2002). Transcutaneous functional electrical stimulator "Compex Motion". Artif. Organs 26, 219–223. doi: 10.1046/j.1525-1594.2002.06934.x

Kim, Y. S., Park, J. H., Choi, S. J., Bae, J. Y., Ahn, D. K., McKemy, D. D., et al. (2014). Central connectivity of transient receptor potential melastatin 8-expressing axons in the brain stem and spinal dorsal horn. PLoS ONE 9:e94080. doi: 10.1371/journal.pone.0094080

Lin, C., Niddam, D. M., and Hsu, M. (2014). Meta-analysis on brain representation of experimental dental pain. J. Dent. Res. 93, 126–133. doi: 10.1177/0022034513512654

Lin, M., Genin, G. M., Xu, F., and Lu, T. (2014). Thermal pain in teeth: electrophysiology governed by thermomechanics. Appl. Mech. Rev. 66, 308011–3080114. doi: 10.1115/1.4026912

Lindstedt, F., Johansson, B., Martinsen, S., Kosek, E., Fransson, P., and Ingvar, M. (2011). Evidence for thalamic involvement in the thermal grill illusion: an FMRI study. PLoS ONE 6:e27075. doi: 10.1371/journal.pone.0027075

Madrid, R., and Pertusa, M. (2013). Intimacies and physiological role of the polymodal cold-397 sensitive ion channel TRPM8. Curr. Top. Membr. 74, 293–324. doi: 10.1016/B978-0-12-800181-3.00011-7

McKemy, D. D. (2007). Temperature sensing across species. Pflügers Archiv. 454, 777–791. doi: 10.1007/s00424-006-0199-6

McKemy, D. D. (2013). The molecular and cellular basis of cold sensation. ACS Chem. Neurosci. 4, 238–247. doi: 10.1021/cn300193h

Megias-Alguacil, D., Keller, T., Lutz, K., Barlow, A. P., and Ettlin, D. A. (2008). Design and construction of a magnetic resonance compatible multi-injector gas jet delivery system. Rev. Sci. Instrum. 79, 14301. doi: 10.1063/1.2823329

Meier, M. L., Brügger, M., Ettlin, D. A., Luechinger, R., Barlow, A., Jäncke, L., et al. (2012). Brain activation induced by dentine hypersensitivity pain–an fMRI study. J. Clin. Periodontol. 39, 441–447. doi: 10.1111/j.1600-051X.2012.01863.x Moana-Filho, E. J., Nixdorf, D. R., Bereiter, D. A., John, M. T., and Harel, N. (2010).

Evaluation of a magnetic resonance-compatible dentoalveolar tactile stimulus device. BMC Neurosci. 11:142. doi: 10.1186/1471-2202-11-142

Moulton, E. A., Schmahmann, J. D., Becerra, L., and Borsook, D. (2010). The cerebellum and pain: passive integrator or active participator? Brain Res. Rev. 65, 14–27. doi: 10.1016/j.brainresrev.2010.05.005

Patapoutian, A., Tate, S., and Woolf, C. J. (2009). Transient receptor potential channels: targeting pain at the source. Nat. Rev. Drug Discov. 8, 55–68. doi: 10.1038/nrd2757

Peyron, R., Laurent, B., and García-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol. Clin. 30, 263–288. doi: 10.1016/S0987-7053(00)00227-6

Pigg, M., Baad-Hansen, L., Svensson, P., Drangsholt, M., and List, T. (2010). Reliability of intraoral quantitative sensory testing (QST). Pain 148, 220–226. doi: 10.1016/j.pain.2009.10.024

Puce, A., Constable, R. T., Luby, M. L., McCarthy, G., Nobre, A. C., Spencer,

D. D., et al. (1995). Functional magnetic resonance imaging of sensory and motor cortex: comparison with electrophysiological localization. J. Neurosurg. 83, 262–270. doi: 10.3171/jns.1995.83.2.0262

Schiff, T., He, T., Sagel, L., and Baker, R. (2006). Efficacy and safety of a novel stabilized stannous fluoride and sodium hexametaphosphate dentifrice for dentinal hypersensitivity. J. Contemp. Dent. Pract. 7, 1–8.

Servos, P., Zacks, J., Rumelhart, D. E., and Glover, G. H. (1998). Somatotopy of the human arm using fMRI. Neuroreport 9, 605–609. doi: 10.1097/00001756- 199803090-00008

Story, G. M., Peier, A. M., Reeve, A. J., Eid, S. R., Mosbacher, J., Hricik, T. R., et al. (2003). ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. Cell 112, 819–829. doi: 10.1016/S0092- 8674(03)00158-2

Svensson, P., Baad-Hansen, L., Pigg, M., List, T., Eliav, E., Ettlin, D., et al. (2011). Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions–a taskforce report. J. Oral Rehabil. 38, 366–394. doi: 10.1111/j.1365-2842.2010.02196.x

Takashima, Y., Daniels, R. L., Knowlton, W., Teng, J., Liman, E. R., and McKemy, D. D. (2007). Diversity in the neural circuitry of cold sensing revealed by genetic axonal labeling of transient receptor potential melastatin 8 neurons. J. Neurosci. 27, 14147–14157. doi: 10.1523/JNEUROSCI.4578-07.2007

Wallois, F., Lebeon, A., and Duron, B. (1997). An improved mechanical air puff stimulator that allows activation of a variety of endoepithelial receptors and is suitable for the study of reflexes in animals and humans. J. Neurosci. Methods 77, 119–127. doi: 10.1016/S0165-0270(97)00116-7

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2.3 *Empirical study 3*

Dentin hypersensitivity monitored by cold air quantitative sensory testing

Monitoring dentine hypersensitivity

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Keywords: Pain, Dentin Sensitivity, Cold temperature, Quantitative sensory testing, Psychophysics, Reliability

Abstract

Background: Quantification of dentin hypersensitivity (DH) is challenging and requires standardized, graded stimulation by natural-like stimuli.

Objective: The present study aimed at identifying DH subjects and longitudinally monitoring their pain thresholds by cold air quantitative sensory testing (QST).

Methods: Subject recruitment started with an online DH questionnaire. Respondents were screened by dental air stimulation. Sensitizing and habituating subjects were excluded. A recently developed stimulation device was employed for cold air QST. Single tooth DH was verified by applying an equi-intense stimulus to a control tooth. Descriptive statistics were applied for subject characteristics. Mean values were calculated for the stimulation parameters temperature and air flow. Reliability of temperatures for detecting pain and for evoking moderate pain over multiple time points within a three weeks period were analyzed by two-way random single and average measures intra-class correlation coefficients.

Results: 353 persons completed the online DH questionnaire of which 117 were screened. 44 passed the screening, yet 15 were excluded for various reasons. 29 subjects were monitored by QST across three weeks. Results revealed a high intra-individual stability of the temperature inducing moderate to strong pain intensity (MPI) (single measures ICC of T_{MPI} 0.83, $p < 0.001$). Mean T_{MPI} was -13.69 °C, yet it highly varied among the 29 subjects (SD±10.04 °C).

Conclusions: Using a novel approach, namely dental QST based on cold air stimuli, we present evidence for temporally stable DH perceptions over a three weeks period. The method fulfills international guideline requirements and is recommendable for obtaining valid results when testing various interventions for DH management.

Background

Pain in general and dentin hypersensitivity (DH) specifically are a personal, complex experience that is impossible to fully share with others, making pain quantification challenging. Nociception is defined as the neural process of encoding noxious stimuli. This process generally relies on activation of specific nociceptors (Hucho und Levine 2007; Landmann et al. 2016). Available evidence attributes a role to transient receptor channels to convey DH, namely TRPM8 located on Aδ- and C-fibers and TRPA1 (Chung et al. 2013; Lin et al. 2014; Ferrandiz-Huertas et al. 2014).

Current methods for assessing DH employ non-gradable mechanical and cold metal/air/ water/ice-stimuli and use response scales that often rely on subject-investigator interaction that lack validation (Schiff et al. 2006). Efforts to activate nociceptors in a standardized and graded manner are evolving and improve with technical innovations. E.g. contact thermal systems based on the Peltier-principle were developed for quantitative sensory testing (QST) (Svensson et al. 2011). Although a small thermode size for intraoral cold stimulation is available, only one single report has hitherto been published that would indicate this system's ability to quantify DH (Rahal et al. 2015). Our group recently reported on a novel, MR-compatible, computer-controlled cold air stimulation apparatus (CASA) for intraoral QST (Bronnimann et al. 2016). Main advantages of the CASA over Peltier element based systems are 1) its lack of tissue contact that otherwise would lead to interaction with a tactile perception (Nolan et al. 2011; Selinger et al. 1994) and 2) its capability to deliver a gradable natural stimulus. This latter aspect is important since external validity in somatosensory research is mainly achieved by the application of natural-like stimuli (Holland et al. 1997). Additionally, most traditional thermal stimulus applications require physical closeness to the examiner which may lead to subject response bias

(Nevin 1969; Sullivan et al. 2004; Sambo et al. 2010; Cano und Williams, Amanda C de C 2010; Kleck et al. 1976; Williams, Amanda C. de C. 2002).

Therefore, the present study aimed at monitor and characterize DH subjects by tracking the pain perception using cold-air-QST across a three weeks period.

Methods

Participants

All participants were recruited by flyers, online-advertisement posted on a publicly accessible online-platform (http://www.markptlatz.uzh.ch) or in a dental office. No subject (min. age: 18 years) had prior knowledge about QST methods. The participants completed an online questionnaire (demographics, dental hygiene habits and tooth sensitivity) (http://www.painresearch.ch/DH, last accessed on Apr. 29th 2018). Subjects had to be in general good health. The participant's selection was based on self-report, medical history, clinical tooth and soft tissue examination by a dentist, and psychophysical screening at the first visit.

The main inclusion criterion was DH to air blasts of at least one tooth and the presence of a tooth not being painful at equi-intense stimulation (control). Exclusion criteria were: dental treatment less than four weeks before screening or during the ongoing study, change of the toothpaste during the last three months, caries, defective restorations, crowns, orthodontic bands, bleeding on probing and periodontal pockets deeper than 3 mm, gross periodontal disease/trauma in the past 12 months, medication and drug intake with possible interaction with pain perception (analgesics, antidepressants, hypnotics). In addition, subjects were excluded when demonstrating habituation/sensitization effects (Overview stimulation procedure Fig. 1).

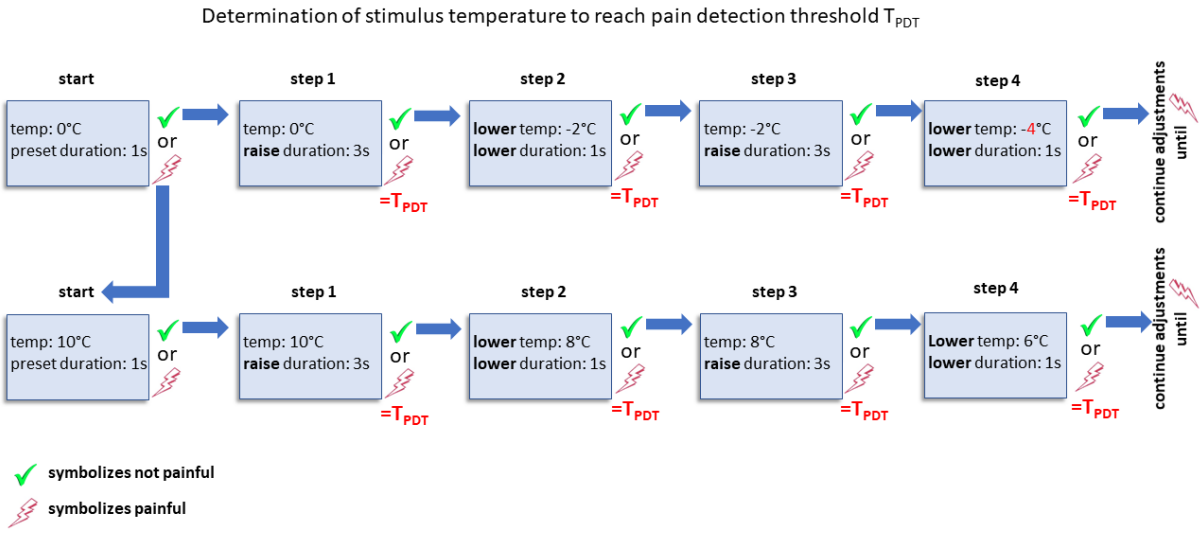

Fig 1: Schematic overview of stimulation procedures: Upper line showing procedure of a subject with no painful sensation at first stimulation (0 °C with 1 s duration), lower line showing procedure applied, when subject already had pain sensation at first stimulation (0 °C with 1 s duration). Technical details of CASA please refer to Brönnimann et al. 2016.

DH screening

Subjects responding with 'yes' or 'uncertain' to the air hypersensitivity item were invited for a screening visit. The CASA was used for hypersensitive tooth-screening among incisors, canines and premolars (Bronnimann et al. 2016). All experiments took place in the Pain Unit lab at the Center of Dental Medicine of the University of Zurich and were conducted by the same examiner (B.B.). Lab environmental temperature was 25.5 °C ± 1 °C.

For DH screening of a single tooth in each participant during a first session, subjects were given a dichotomous oral response option: 'not painful' and 'painful'. Upon a painful response, subjects were additionally asked to freely describe the pain quality and to select an item on a list (Items Fig. 4). The DH assessment was performed by delivering room temperature air blasts at a flow rate of 5 l/min (labial/buccal of dental crown neck) for 3 s (unless subjects reported pain earlier). For this, the examiner held the ending of an air conducting silicone tube of 2 mm

diameter approximately 1 mm away from the tooth (adjacent teeth covered by examiner's index and middle fingers). After each stimulation, the quadrant was switched to minimize sensitization-effects of a quadrant.

After identification of a painful tooth ('target tooth') and a non-painful control tooth in the contralateral quadrant (whenever possible its analogue), the two teeth were further probed for sensitization/habituation: A modified version of the pain scale was employed as it has been shown to be particularly sensitive to changes in perception (Borg 1998; Bronnimann et al. 2016).

Both the target and control tooth were alternately stimulated ten times with an inter-stimulus interval (ISI) of approximately 10 s. Subjects with ≥ 2 scale steps (modified Borg scale, Fig. 2) or similar ratings between target and control teeth were excluded.

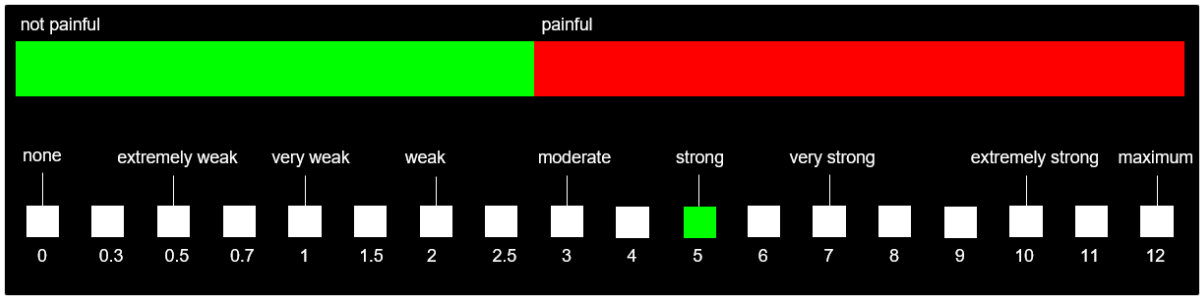

Fig 2. Adapted version of the Borg pain scale, operated by the subject with a trackball after each stimulus (pain threshold > 2.5). On this figure, stimulus intensity was exemplarily set to "5/ strong perception" (green square). MPI was defined as rating of 4 to 5.

Questionnaires

Subjects included in the DH monitoring study phase completed the following psychometric questionnaires: *Dental Hypersensitivity Experience Questionnaire* (DHEQ) (Boiko et al. 2010),

Dental Anxiety Scale (DAS), *State/Trait Anxiety Inventory* (STAI) (Corah 1969; Spielberger 2010; Corah et al. 1978), *Pain catastrophizing scale* (PCS) (Sullivan et al. 1995a; Meyer et al. 2008).

DH monitoring by QST

Subsequent to the DH screening appointment, dental QST was additionally performed three times over a three-week period (Fig. 1) using the modified Borg scale (Fig. 2). Technical details and procedural steps (CASA) have been previously reported (Bronnimann et al. 2016). Each test session was scheduled between noon and 7 pm.

First QST session

Before each QST session, subjects were instructed in a standardized manner regarding the rating procedure. To familiarize subjects with the stimulus, a weak air blast (5 l/min) of 0 °C ± 2 °C was applied to the subject's hand. Subjects then laid in supine position on a dental chair with the cold exchanger of the CASA mounted contactless above them. The stimulation tube was held next to the target tooth by a dental splint, which protected surrounding structures from the stimulus. The ears of subjects were covered by noise canceling headphones (Bose® Quiet-Comfort 25) to eliminate auditory inputs.

Subsequently, the air temperature was constantly modified with the aim to identify the minimal temperature 1) to reach the pain detection threshold (T_{PDT}) and 2) to determine the moderate pain intensity threshold on the target tooth, rated 4-5 on the Borg scale (T_{MPI}). Both thresholds were calculated as the average of three consecutive measurements. The procedure started with a 1 s air blast of 3 l/min at 0° ± 2° C which was applied to the target tooth. If this first stimulus already evoked pain, the flow rate was lowered to 1 l/min and the temperature was increased to 10° ± 2° C. For the subsequent air blasts, the flow rate (in increments of 1-2 l/min. to a max. of 17 l/min), the stimulus duration (up to 3 s) were constantly modified to reach T_{PDT}

and T_{MPI}. If T_{PDT} and T_{MPI} were not reached, the temperature was lowered by 2° ± 1° C and the same procedure was repeated. The ISI varied between 10-60 s, depending on the temperature adjusting time of CASA . T_{MPI} data reported in Fig. 5 show the temperature evoking pain after repeated consecutive stimulations.

Next, the examiner repositioned the air delivery tube for stimulating the control tooth, which was stimulated three times with T_{MPI} of the target tooth. Overall, this first QST session lasted 30 min. ± 5 min. At the end of the first QST session, subjects completed a brief questionnaire concerning location and time course of somatosensory sensation at moderate pain level and pain characteristics including the verbal pain descriptors presented by Beissner et al. (2010) and possible paradoxical warm or heat sensation.

Second and third QST sessions

The initial stimulus temperature at the consecutive measurements (weeks two and three) was individually set at T_{PDT} of the previous measurement + 10 °C ± 2 above the T_{PDT}. The same procedure was applied as described in 2.5.1. These QST sessions lasted 20 min. ± 5 min.

Statistical analysis

Descriptive statistics were applied for subject characteristics. Mean and SD values were calculated for flow rate and temperature evoking T_{PDT} and T_{MPI}.Reliability of T_{PDT} and T_{MPI} over the three weeks period were analyzed by using two-way random single and average measures intra-class correlation coefficient (ICC).

Gender differences were calculated by a t-test of independent samples. Possible correlations between age and T_{MPI} were calculated by Pearson-Bravais correlation. Correlations between psychometric values and painful temperatures were calculated by Spearman's test. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS 23, Windows version, SPSS Inc., USA).

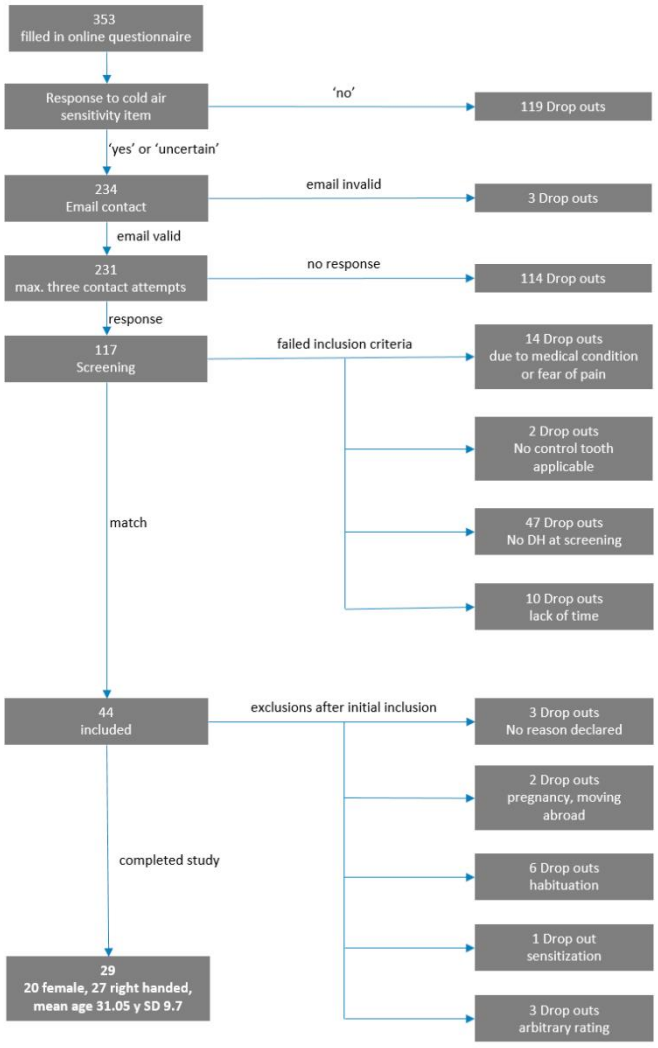

Fig 3. Flow chart of recruitment process and dropouts

Results

Recruitment

353 individuals completed the online DH questionnaire of which 117 were screened. 44 passed the screening, yet 15 were excluded for various reasons. 29 subjects (20 female, 27 right handed, mean age = 31.05 years, SD± 9.7, age range = 20 - 52 years) met the inclusion criteria and completed all QST measurements. Details of the recruitment process are listed in Fig. 3.

Questionnaires

The mean DAS score was 9.8 (SD± 3.1), mean state score 36.0 (SD ±8.1), mean trait score 35.7 (SD ±7.8), mean DHEQ score 62.7 (SD ±14.0) and mean PCS score 20.0 (SD ±9.3). None of the psychometric assessments correlated significantly with T_{PDT}, T_{MPI}, age or gender ($p > 0.05$).

Repeated QST

All subjects confirmed that the applied air blasts were only felt at the designated tooth. Air stimuli at temperatures < 15 °C were described as cool, cold or icy. No paradoxical heat sensation was reported (Fig. 4). All participants declared that the stimuli reminded them of cold stimuli experienced in everyday life.

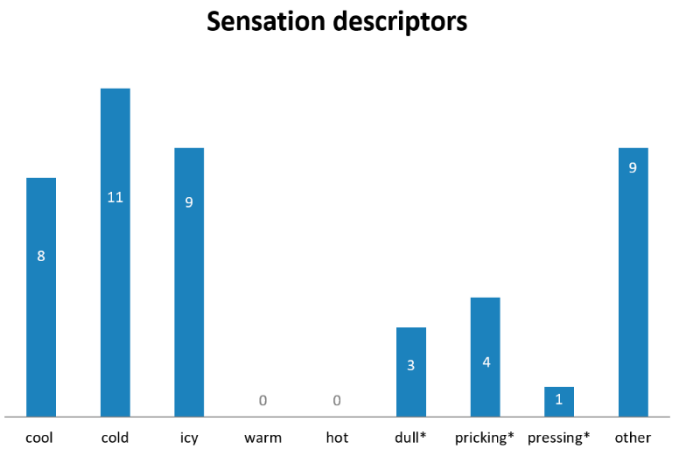

Fig. 4. Frequency of subjects' pain descriptors, which were presented immediately after the first measurement (multiple answers were possible). 'Other' items reported were: pulling (3), stinging (3), pulsating (2), 'like a contraction in the tissue' (1). *) Items validated by Beissner (2010).

The means over all three measurements of T_{PDT} and T_{MPI} were -7.04 °C, (SD ±10.80) and -13.69 °C (SD±10.04), respectively. The overall mean air flow rate of all measurements was 9.14 l/min. (SD ±3.26). Painful sensations always remitted prior to the application of the consecutive stimulus. Stimulus duration for T_{MPI} was 1 s in two subjects, 2 s in two subjects and 3 s in 25 subjects. No significant differences were noted for T_{PDT} and T_{MPI} concerning gender, air flow rate and stimulus duration ($p > 0.05$). Correlation of age and T_{MPI} ($r's > .133$, $p's > 0.493$) and T_{PDT} ($r's > 0.223$, $p's > 0.246$) was not significant at any timepoint.

Reliability

Single measures ICC of T_{PDT} over three weeks was 0.78,($p < 0.001$), average measures ICC was 0.91 ($p < 0.001$). Single measures ICC of T_{MPI} over three weeks was 0.83 ($p < 0.001$), average measures ICC of T_{MPI} over the same period was 0.98, $p < 0.001$(Fig. 5).

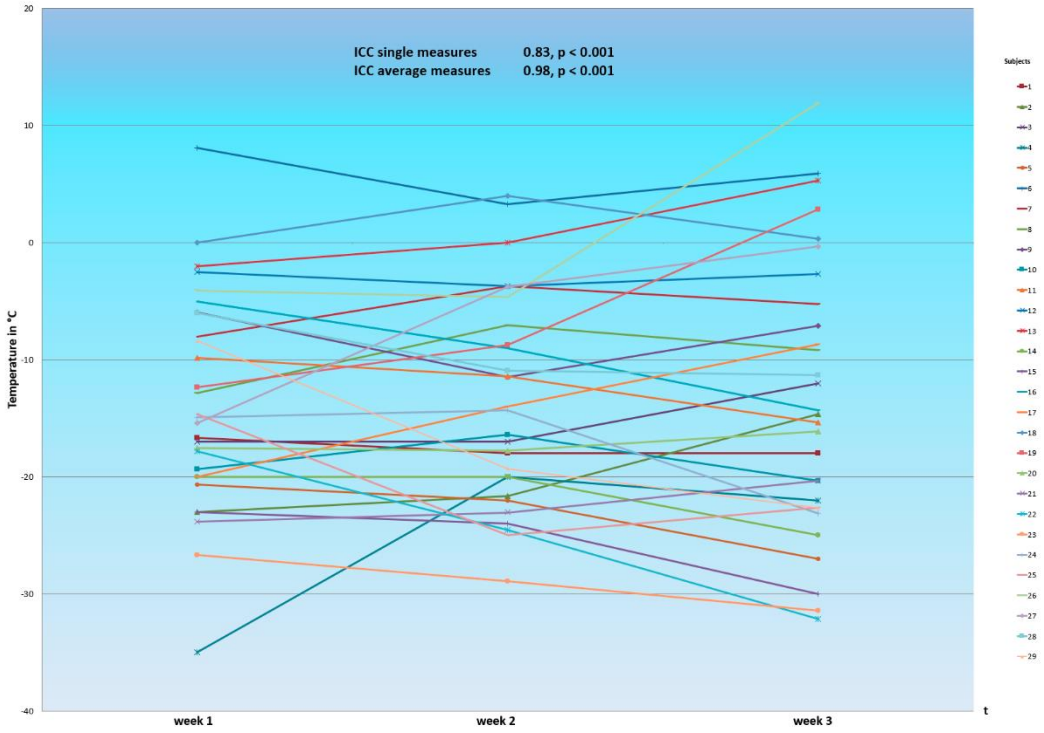

Fig. 5. Reliability of T_{MPI} over three weeks: Each dot represents the temperature evoking moderate to strong pain on the hypersensitive tooth (mod. Borg Scale 4-5). At each measurement timepoint, after the determination of TMPI the hypersensitive tooth was stimulated 10 times in a row with an interstimulus interval of 10 ± 2 s in order to reinsure for perception stability within the same measurement.

Discussion

The recruitment process and the dropout rate in this study show that DH is associated with a highly volatile pain state, which poses a major challenge to evaluation of perception and consequently for intervention studies: Pre-treatment perception stability is an important prerequisite for enhancing the reliability of DH intervention studies. It is therefore vital to explore novel approaches for quantifying sensory perceptions related to DH.

For the first time, this study shows evidence for temporally stable intra-individual sensory perceptions related to DH, provided by a novel approach using dental QST based on natural, non-

contact air stimuli at temperatures mainly below 0°C. At these temperatures TRPM8 located on Aδ- and C-fibers and TRPA1 are potentially triggered which may play a major role in cold induced DH.

The study procedure involved 1) an online DH questionnaire, 2) screening of potential DH by the application of a natural air stimulus using a novel cold air application device (CASA) (Bronnimann et al. 2016), and 3) testing for sensitizing and habituation effects using a modified rating scale (Borg 1998). DH was verified in each subject by applying an equi-intense T_{MPI} stimulus assessed at the target tooth to a control tooth. The QST results revealed (Fig. 5): stable intra-individual pain thresholds over a three weeks period whereas a high inter-individual variability regarding DH pain evoking temperatures was. Finally, external validity of the stimulus type provided by CASA was evidenced by the subjects' reports that the stimulus evoked a familiar cold perception as commonly experienced in everyday life.

Recruitment process

Self-selection bias is generally considered a crucial challenge in the study recruitment process, especially for studies investigating pain conditions (Heckman 1977). E.g., subjects suffering from severe DH may have avoided participation due to fear of pain, supported by the fact that fear of dental pain is associated with stronger conditioniability compared to other body parts (Meier et al. 2014). Of the 353 individuals completing the online DH questionnaire, two thirds (66%) responded positively to the air sensitivity item, yet only half of them appeared to the screening visit. A large proportion (40%) failed to respond with DH at the initial appointment, suggesting that either DH resolved or that the primary motivation might have been the monetary incentive (Tishler und Bartholomae 2002). 44 subjects passed the screening, but 10 of them (23%) needed to be excluded due to habituation or sensitization (10). In the end, 29

subjects (8%) of the initial 353 candidates formed the study population that was monitored by QST across three weeks.

DH monitoring

Inter-individual variability of T_{MPI} was remarkably high, which might be explained by various influences, including differences in tooth morphology and individual response biases. Repeated assessment of T_{MPI} over time revealed a high intra-individual. Age and gender did not show any correlation with T_{MPI}. The latter findings contrasts with the report by Rolke's et al. (2006), in which threshold alterations over time correlated with age and gender, namely the cold pain thresholds raised with age and thresholds for women were significantly lower than for men. However, Rolke et al. stated that body location has a much greater effect on the thresholds than age and gender.

Reliability studies on reporting scales and stimulation methods currently employed in DH intervention studies are scarce. The characteristics of our tool allow to run protocols, that can mimic natural-like stimulation situations. The CASA has the advantage to comply with international recommendations(Holland et al. 1997) and offers a higher validity of intervention studies. Further, the use of response scales often rely on subject-investigator interaction lack validation(Schiff et al. 2006). CASA allows with its experimental setting a more investigator-independent assessment of perception. A direct comparison of our method and protocols used in intervention studies is required.

Considering stimulus perceptions, no paradoxical warm or heat sensations were reported by our subjects. Absence of such perceptions indicates proper functioning of Aδ fibers (Susser et al. 1999).

Psychometric data

Psychometric assessment take into account potential psychological pain threshold modulators (Newton und Buck 2000). The scales used in the current study were previously reported to be sensitive to pain thresholds (Sullivan et al. 1995a). T_{MPI} showed no significant correlations with the reported everyday burden of DH, anxiety and catastrophizing, indicating that in this selected group of subjects, dentin hypersensitivity did not have any major psychological effect on their everyday life. Assumingly subjects with high sensitivity scores were excluded from the study. As discussed above, self-selection bias might have filtered out potentially high scoring subjects on anxiety scales. Morphological features might have a bigger impact on T_{MPI} than psychological factors. We expected a negative correlation of T_{MPI} and DHEQ measures, which could not be confirmed. This finding corresponds to Melzack's (1975a) comment on pain scaling, that perceived pain intensity does not necessarily vary with stimulus strength (T_{MPI} in our study), but depends on the quality of the experience and location of application.

Limitations

CASA did not allow a randomized design for controlling for attention and anticipation processes (Ploghaus 1999; Fairhurst et al. 2007). The subjects always were aware which tooth was stimulated. Psychophysical data in this study are not normative values but present inter- and intra-individual differences within a selected cohort.

Conclusion

Standardized algesimetry per se is still a challenge with regard to the multidimensionality of the pain experience. In respect of this fact, quantification of pain in DH presents a special challenge with its high volatile phenomenology. Furthermore, current DH assessment methods use non-variable temperature stimuli in non-standardized environments. Here, we present a novel

dental QST approach based on controlled, graded cold air stimuli. Results revealed that DH related perceptions can be reliably assessed, characterized by high intra-individual DH perceptions over a three weeks period in a selected subgroup. The method thus fulfills important guideline requirements and is recommendable for obtaining valid results when testing various interventions for DH management (Svensson et al. 2011).

Ethical approval

In agreement with the 1964 Declaration of Helsinki, the Regional Ethics Review Board at University of Zurich approved the study (KEK-ZH-Nr. 2010-0347) and all participants signed an informed-consent. The subjects were monetarily compensated for study participation.

Conflicts of Interest and Source of Funding

This research project was supported by GlaxoSmithKline, Consumer Healthcare, Weybridge, UK. C. Parkinson is an employee of the sponsor, GSK. All other authors declare that they have no other link to this company and thus no conflicts of interests.

Acknowledgements

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References

Alvarado, Lisa T.; Perry, Griffin M.; Hargreaves, Kenneth M.; Henry, Michael A. (2007): TRPM8 Axonal expression is decreased in painful human teeth with irreversible pulpitis and cold hyperalgesia. In: *Journal of endodontics* 33 (10), S. 1167–1171. DOI: 10.1016/j.joen.2007.06.018.

Anand, K. J. S.; Hall, R. Whit (2007): Controversies in neonatal pain: an introduction. In: *Seminars in perinatology* 31 (5), S. 273–274. DOI: 10.1053/j.semperi.2007.07.014.

Apkarian, A. Vania; Bushnell, M. Catherine; Treede, Rolf-Detlef; Zubieta, Jon-Kar (2005): Human brain mechanisms of pain perception and regulation in health and disease. In: *European journal of pain (London, England)* 9 (4), S. 463–484. DOI: 10.1016/j.ejpain.2004.11.001.

Apkarian, A. Vania; Stea, Richard A.; Bolanowski, Stanley J. (2009): Heat-Induced Pain Diminishes Vibrotactile Perception. A Touch Gate. In: *Somatosensory & Motor Research* 11 (3), S. 259–267. DOI: 10.3109/08990229409051393.

AWMF (1962/2018): AWMF: Leitlinien-Suche. Online verfügbar unter https://www.awmf.org/leitlinien/leitlinien-suche.html, zuletzt geprüft am 10.08.2018.

Backonja, Miroslav Misha; Attal, Nadine; Baron, Ralf; Bouhassira, Didier; Drangholt, Mark; Dyck, Peter J. et al. (2013): Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. In: *Pain* 154 (9), S. 1807–1819. DOI: 10.1016/j.pain.2013.05.047.

Baker, Rose; Jackson, Dan (2006): Using journal impact factors to correct for the publication bias of medical studies. In: *Biometrics* 62 (3), S. 785–792. DOI: 10.1111/j.1541-0420.2005.00513.x.

Baliki, Marwan N.; Apkarian, A. Vania (2015): Nociception, Pain, Negative Moods, and Behavior Selection. In: *Neuron* 87 (3), S. 474–491. DOI: 10.1016/j.neuron.2015.06.005.

Bartold, P. M. (2006): Dentinal hypersensitivity. A review. In: *Australian Dental Journal* 51 (3), S. 212–218. DOI: 10.1111/j.1834-7819.2006.tb00431.x.

Basbaum, Allan I.; Bautista, Diana M.; Scherrer, Grégory; Julius, David (2009): Cellular and molecular mechanisms of pain. In: *Cell* 139 (2), S. 267–284. DOI: 10.1016/j.cell.2009.09.028.

Beissner, Florian; Brandau, Amadeus; Henke, Christian; Felden, Lisa; Baumgärtner, Ulf; Treede, Rolf-Detlef et al. (2010): Quick Discrimination of Adelta and C Fiber Mediated Pain Based on Three Verbal Descriptors. In: *PloS one* 5 (9), S. e12944. DOI: 10.1371/journal.pone.0012944.

Belfer, Inna (2013): Nature and nurture of human pain. In: *Scientifica* 2013, S. 415279. DOI: 10.1155/2013/415279.

Binshtok, Alexander M. (2011): Mechanisms of nociceptive transduction and transmission: a machinery for pain sensation and tools for selective analgesia. In: *International review of neurobiology* 97, S. 143–177. DOI: 10.1016/B978-0-12-385198-7.00006-0.

Blankenbaker, Donna G.; Ullrick, Steven R.; Davis, Kirkland W.; Smet, Arthur A. de; Haaland, Ben; Fine, Jason P. (2008): Correlation of MRI findings with clinical findings of trochanteric pain syndrome. In: *Skeletal radiology* 37 (10), S. 903–909. DOI: 10.1007/s00256-008-0514-8.

Boiko, Olga V.; Baker, Sarah R.; Gibson, Barry J.; Locker, David; Sufi, Farzana; Barlow, Ashley P. S.; Robinson, Peter G. (2010): Construction and validation of the quality of life measure for dentine hypersensitivity (DHEQ). In: *Journal of clinical periodontology* 37 (11), S. 973–980. DOI: 10.1111/j.1600-051X.2010.01618.x.

Borg, Gunnar (1998): Borg's perceived exertion and pain scales: Human kinetics.

Bräscher, Anne-Kathrin; Becker, Susanne; Hoeppli, Marie-Eve; Schweinhardt, Petra (2016): Different Brain Circuitries Mediating Controllable and Uncontrollable Pain. In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 36 (18), S. 5013–5025. DOI: 10.1523/JNEUROSCI.1954-15.2016.

Brembs, Björn (2018): Prestigious Science Journals Struggle to Reach Even Average Reliability. In: *Frontiers in human neuroscience* 12, S. 37. DOI: 10.3389/fnhum.2018.00037.

Bronnimann, Ben; Meier, Michael L.; Hou, Mei-Yin; Parkinson, Charles; Ettlin, Dominik A. (2016): Novel Air Stimulation MR-Device for Intraoral Quantitative Sensory Cold Testing. In: *Frontiers in human neuroscience* 10, S. 335. DOI: 10.3389/fnhum.2016.00335.

Brügger, M.; Lutz, K.; Brönnimann, B.; Meier, M. L.; Luechinger, R.; Barlow, A. et al. (2012): Tracing toothache intensity in the brain. In: *Journal of dental research* 91 (2), S. 156–160. DOI: 10.1177/0022034511431253.

Brügger, Mike; Ettlin, Dominik A.; Meier, Michael; Keller, Thierry; Luechinger, Roger; Barlow, Ashley et al. (2011): Taking Sides with Pain - Lateralization aspects Related to Cerebral Processing of Dental Pain. In: *Frontiers in human neuroscience* 5, S. 12. DOI: 10.3389/fnhum.2011.00012.

Cano, Annmarie; Williams, Amanda C de C (2010): Social interaction in pain: reinforcing pain behaviors or building intimacy? In: *Pain* 149 (1), S. 9–11. DOI: 10.1016/j.pain.2009.10.010.

Chung, G.; Jung, S. J.; Oh, S. B. (2013): Cellular and Molecular Mechanisms of Dental Nociception. In: *Journal of dental research* 92 (11), S. 948–955. DOI: 10.1177/0022034513501877.

Colloca, Luana; Benedetti, Fabrizio (2007): Nocebo hyperalgesia: how anxiety is turned into pain. In: *Current opinion in anaesthesiology* 20 (5), S. 435–439. DOI: 10.1097/ACO.0b013e3282b972fb.

Corah, N. L. (1969): Development of a dental anxiety scale. In: *Journal of dental research* 48 (4), S. 596.

Corah, Norman L.; Gale, Elliot N.; Illig, Stephen J. (1978): Assessment of a dental anxiety scale. In: *The Journal of the American Dental Association* 97 (5), S. 816–819. DOI: 10.14219/jada.archive.1978.0394.

Craig, A. D. (2002): How do you feel? Interoception: the sense of the physiological condition of the body. In: *Nature reviews. Neuroscience* 3 (8), S. 655–666. DOI: 10.1038/nrn894.

Craig, A. D. (2003): A new view of pain as a homeostatic emotion. In: *Trends in neurosciences* 26 (6), S. 303–307.

Dababneh, R. H.; Khouri, A. T.; Addy, M. (1999): dentine hypersensitivity. Dentine hypersensitivity — an enigma? a review of terminology, mechanisms, aetiology and management. In: *Br Dent J* 187 (11), S. 606–611. DOI: 10.1038/sj.bdj.4800345.

DaSilva, Alex F. M.; Becerra, Lino; Makris, Nikos; Strassman, Andrew M.; Gonzalez, R. Gilberto; Geatrakis, Nina; Borsook, David (2002): Somatotopic activation in the human trigeminal pain pathway. In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 22 (18), S. 8183–8192.

Elsevier; Franklin, Jennifer (2018): Results masked review: peer review without publication bias. Online verfügbar unter https://www.elsevier.com/connect/reviewers-update/results-

masked-review-peer-review-without-publication-bias, zuletzt aktualisiert am 11.09.2018, zuletzt geprüft am 12.09.2018.

Ettlin, D. A.; Brügger, M.; Keller, T.; Luechinger, R.; Jäncke, L.; Palla, S. et al. (2009): Interindividual differences in the perception of dental stimulation and related brain activity. In: *European journal of oral sciences* 117 (1), S. 27–33. DOI: 10.1111/j.1600-0722.2008.00590.x.

Ettlin, D. A.; Zhang, H.; Lutz, K.; Järmann, T.; Meier, D.; Gallo, L. M. et al. (2004): Cortical activation resulting from painless vibrotactile dental stimulation measured by functional magnetic resonance imaging (FMRI). In: *Journal of dental research* 83 (10), S. 757–761. DOI: 10.1177/154405910408301004.

Fairhurst, Merle; Wiech, Katja; Dunckley, Paul; Tracey, Irene (2007): Anticipatory brainstem activity predicts neural processing of pain in humans. In: *Pain* 128 (1-2), S. 101–110. DOI: 10.1016/j.pain.2006.09.001.

Ferrandiz-Huertas, Clotilde; Mathivanan, Sakthikumar; Wolf, Christoph Jakob; Devesa, Isabel; Ferrer-Montiel, Antonio (2014): Trafficking of ThermoTRP Channels. In: *Membranes* 4 (3), S. 525–564. DOI: 10.3390/membranes4030525.

Ferrari, Marco; Quaresima, Valentina (2012): A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. In: *NeuroImage* 63 (2), S. 921–935. DOI: 10.1016/j.neuroimage.2012.03.049.

Garcia-Larrea, Luis; Peyron, Roland (2013): Pain matrices and neuropathic pain matrices: a review. In: *Pain* 154 Suppl 1, S29-43. DOI: 10.1016/j.pain.2013.09.001.

Gneezy, Uri; Meier, Stephan; Rey-Biel, Pedro (2011): When and Why Incentives (Don't) Work to Modify Behavior. In: *Journal of Economic Perspectives* 25 (4), S. 191–210. DOI: 10.1257/jep.25.4.191.

Gruss, Sascha; Treister, Roi; Werner, Philipp; Traue, Harald C.; Crawcour, Stephen; Andrade, Adriano; Walter, Steffen (2015): Pain Intensity Recognition Rates via Biopotential Feature Patterns with Support Vector Machines. In: *PloS one* 10 (10), e0140330. DOI: 10.1371/journal.pone.0140330.

Harzing Anne-Wil (2017): Publish or Perish: Realising Google Scholar’s potential to democratise citation analysis. https://harzing.com/download/gsday_madrid.pdf. Online verfügbar unter https://harzing.com/download/gsday_madrid.pdf, zuletzt geprüft am 19.09.2018.

Heckman, James J. (1977): Sample selection bias as a specification error (with an application to the estimation of labor supply functions): National Bureau of Economic Research Cambridge, Mass., USA.

Higgins, E. Tory (1997): Beyond pleasure and pain. In: *American Psychologist* 52 (12), S. 1280–1300. DOI: 10.1037/0003-066X.52.12.1280.

Holland, G. R.; Narhi, M. N.; Addy, M.; Gangarosa, L.; Orchardson, R. (1997): Guidelines for the design and conduct of clinical trials on dentine hypersensitivity*. In: *Journal of clinical periodontology* 24 (11), S. 808–813. DOI: 10.1111/j.1600-051X.1997.tb01194.x.

Hu, Li; Iannetti, Gian Domenico (2016): Painful Issues in Pain Prediction. In: *Trends in neurosciences* 39 (4), S. 212–220. DOI: 10.1016/j.tins.2016.01.004.

Hucho, Tim; Levine, Jon D. (2007): Signaling pathways in sensitization: toward a nociceptor cell biology. In: *Neuron* 55 (3), S. 365–376. DOI: 10.1016/j.neuron.2007.07.008.

IASP (1994): IASP Terminology - IASP. Online verfügbar unter http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Pain, zuletzt aktualisiert am 2017, zuletzt geprüft am 19.09.2018.

Johnston, Mary E. (1994): Effects of Computer-based Clinical Decision Support Systems on Clinician Performance and Patient Outcome: A Critical Appraisal of Research. In: *Ann Intern Med* 120 (2), S. 135. DOI: 10.7326/0003-4819-120-2-199401150-00007.

Kállai, Ibolya; Barke, Antonia; Voss, Ursula (2004): The effects of experimenter characteristics on pain reports in women and men. In: *Pain* 112 (1-2), S. 142–147. DOI: 10.1016/j.pain.2004.08.008.

Kim, Yun Sook; Park, Jun Hong; Choi, Su Jung; Bae, Jin Young; Ahn, Dong Kuk; McKemy, David D.; Bae, Yong Chul (2014): Central connectivity of transient receptor potential melastatin 8-expressing axons in the brain stem and spinal dorsal horn. In: *PloS one* 9 (4), e94080. DOI: 10.1371/journal.pone.0094080.

Kleck, Robert E.; Vaughan, Robert C.; Cartwright-Smith, Jeffrey; Vaughan, Katherine Burns; Colby, Carl Z.; Lanzetta, John T. (1976): Effects of being observed on expressive, subjective, and physiological responses to painful stimuli. In: *Journal of Personality and Social Psychology* 34 (6), S. 1211–1218. DOI: 10.1037/0022-3514.34.6.1211.

Kröner-Herwig, B. (2014): Einfluss von kognitiv-emotionalen Prozessen auf Schmerz und Funktionsbeeinträchtigung. Eine psychobiologische Perspektive. In: *Schmerz (Berlin, Germany)* 28 (5), 537-44; quiz 545-6. DOI: 10.1007/s00482-014-1468-5.

Kuijpers, T.; van Middelkoop, M.; Rubinstein, S. M.; Ostelo, R.; Verhagen, A.; Koes, B. W.; van Tulder, M. W. (2011): A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. In: *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 20 (1), S. 40–50. DOI: 10.1007/s00586-010-1541-4.

Landmann, Gunther; Stockinger, Lenka; Lustenberger, Corinne; Schmelz, Martin; Rukwied, Roman (2016): Effects of Current Density on Nociceptor Activation Upon Electrical Stimulation in Humans. In: *Pain practice : the official journal of World Institute of Pain* 16 (3), S. 273–281. DOI: 10.1111/papr.12339.

Legrain, Valéry; Iannetti, Gian Domenico; Plaghki, Léon; Mouraux, André (2011): The pain matrix reloaded: a salience detection system for the body. In: *Progress in Neurobiology* 93 (1), S. 111–124. DOI: 10.1016/j.pneurobio.2010.10.005.

Lieberman, Matthew D.; Eisenberger, Naomi I. (2015): The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference. In: *Proceedings of the National Academy of Sciences of the United States of America* 112 (49), S. 15250–15255. DOI: 10.1073/pnas.1515083112.

Lin, Min; Genin, Guy M.; Xu, Feng; Lu, TianJian (2014): Thermal Pain in Teeth: Electrophysiology Governed by Thermomechanics. In: *Applied mechanics reviews* 66 (3), S. 308011–3080114. DOI: 10.1115/1.4026912.

Logan, Deirdre E.; Claar, Robyn Lewis; Scharff, Lisa (2008): Social desirability response bias and self-report of psychological distress in pediatric chronic pain patients. In: *Pain* 136 (3), S. 366–372. DOI: 10.1016/j.pain.2007.07.015.

McCracken, Lance M.; Vowles, Kevin E.; Eccleston, Christopher (2004): Acceptance of chronic pain: component analysis and a revised assessment method. In: *Pain* 107 (1), S. 159–166. DOI: 10.1016/j.pain.2003.10.012.

McEwen, Bruce S. (1998): Stress, Adaptation, and Disease: Allostasis and Allostatic Load. In: *Annals of the New York Academy of Sciences* 840 (1), S. 33–44. DOI: 10.1111/j.1749-6632.1998.tb09546.x.

McEwen, Bruce S. (2008): Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. In: *European journal of pharmacology* 583 (2-3), S. 174–185. DOI: 10.1016/j.ejphar.2007.11.071.

Meier, Michael L.; Brügger, Michael; Ettlin, Dominik A.; Luechinger, Roger; Barlow, Ashley; Jäncke, Lutz; Lutz, Kai (2012): Brain activation induced by dentine hypersensitivity pain--an fMRI study. In: *Journal of clinical periodontology* 39 (5), S. 441–447. DOI: 10.1111/j.1600-051X.2012.01863.x.

Meier, Michael L.; de Matos, Nuno M P; Brugger, Mike; Ettlin, Dominik A.; Lukic, Nenad; Cheetham, Marcus et al. (2014): Equal pain-Unequal fear response: enhanced susceptibility of tooth pain to fear conditioning. In: *Frontiers in human neuroscience* 8, S. 526. DOI: 10.3389/fnhum.2014.00526.

Melzack, R.; Wall, P. D. (1965): Pain Mechanisms. A New Theory. In: *Science* 150 (3699), S. 971–978. DOI: 10.1126/science.150.3699.971.

Melzack, Ronald (1975a): The McGill Pain Questionnaire. Major properties and scoring methods. In: *Pain* 1 (3), S. 277–299. DOI: 10.1016/0304-3959(75)90044-5.

Melzack, Ronald (1975b): The McGill Pain Questionnaire: Major properties and scoring methods. In: *Pain* 1 (3), S. 277–299. DOI: 10.1016/0304-3959(75)90044-5.

Meyer, Kathrin; Sprott, Haiko; Mannion, Anne Frances (2008): Cross-cultural adaptation, reliability, and validity of the German version of the Pain Catastrophizing Scale. In: *Journal of psychosomatic research* 64 (5), S. 469–478. DOI: 10.1016/j.jpsychores.2007.12.004.

Millan, Mark J. (1999): The induction of pain: an integrative review. In: *Progress in Neurobiology* 57 (1), S. 1–164. DOI: 10.1016/S0301-0082(98)00048-3.

Mogil, Jeffrey S. (2012): Pain genetics: past, present and future. In: *Trends in genetics : TIG* 28 (6), S. 258–266. DOI: 10.1016/j.tig.2012.02.004.

Morley, Stephen; Eccleston, Christopher; Williams, Amanda (1999): Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour

therapy for chronic pain in adults, excluding headache. In: *Pain* 80 (1), S. 1–13. DOI: 10.1016/S0304-3959(98)00255-3.

Morley, Stephen; Williams, Amanda (2015): New Developments in the Psychological Management of Chronic Pain. In: *Canadian journal of psychiatry. Revue canadienne de psychiatrie* 60 (4), S. 168–175. DOI: 10.1177/070674371506000403.

Naranayan, M. P. (1985): Managerial Incentives for Short-term Results. In: *The Journal of Finance* 40 (5), S. 1469–1484. DOI: 10.1111/j.1540-6261.1985.tb02395.x.

Nevin, John A. (1969): Signal detection theory and operant behaviorA review of David M. Green and John A. Swets' Signal detection theory and psychophysics1. In: *J Exp Anal Behav* 12 (3), S. 475–480. DOI: 10.1901/jeab.1969.12-475.

Newcombe, Nora S.; Bouton, Mark E. (2009): Masked Reviews Are Not Fairer Reviews: SAGE PublicationsSage CA: Los Angeles, CA. Online verfügbar unter http://journals.sagepub.com/doi/abs/10.1111/j.1745-6924.2009.01102.x, zuletzt aktualisiert am 01.01.2009, zuletzt geprüft am 26.08.2018.

Newton, J. Timothy; Buck, Dave J. (2000): Anxiety and Pain Measures in Dentistry. A Guide to their Quality and Application. In: *The Journal of the American Dental Association* 131 (10), S. 1449–1457. DOI: 10.14219/jada.archive.2000.0056.

NICE guidelines (1999/2018): Search Results. NICE. Online verfügbar unter https://www.nice.org.uk/search?q=pain, zuletzt geprüft am 10.08.2018.

Nolan, Todd A.; Hester, Jordan; Bokrand-Donatelli, Yvonne; Caudle, Robert M.; Neubert, John K. (2011): Adaptation of a novel operant orofacial testing system to characterize both mechanical and thermal pain. In: *Behavioural brain research* 217 (2), S. 477–480. DOI: 10.1016/j.bbr.2010.10.022.

Noseda, Rodrigo; Burstein, Rami (2013): Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. In: *Pain* 154, S44-S53. DOI: 10.1016/j.pain.2013.07.021.

Ogawa, S.; Lee, T. M.; Kay, A. R.; Tank, D. W. (1990): Brain magnetic resonance imaging with contrast dependent on blood oxygenation. In: *Proceedings of the National Academy of Sciences* 87 (24), S. 9868–9872. DOI: 10.1073/pnas.87.24.9868.

Ohrbach, Richard; Crow, Heidi; Kamer, Angela (1998): Examiner expectancy effects in the measurement of pressure pain thresholds. In: *Pain* 74 (2), S. 163–170. DOI: 10.1016/S0304-3959(97)00174-7.

Paulson, Pamela E.; Minoshima, Satoshi; Morrow, Thomas J.; Casey, Kenneth L. (1998): Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. In: *Pain* 76 (1), S. 223–229. DOI: 10.1016/S0304-3959(98)00048-7.

Peyron, R.; Laurent, B.; García-Larrea, L. (2000): Functional imaging of brain responses to pain. A review and meta-analysis (2000). In: *Neurophysiologie Clinique/Clinical Neurophysiology* 30 (5), S. 263–288. DOI: 10.1016/S0987-7053(00)00227-6.

Ploghaus, A. (1999): Dissociating Pain from Its Anticipation in the Human Brain. In: *Science* 284 (5422), S. 1979–1981. DOI: 10.1126/science.284.5422.1979.

Poldrack, Russell A. (2006): Can cognitive processes be inferred from neuroimaging data? In: *Trends in cognitive sciences* 10 (2), S. 59–63. DOI: 10.1016/j.tics.2005.12.004.

Price, Donald D.; Bush, Francis M.; Long, Stephen; Harkins, Stephen W. (1994): A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. In: *Pain* 56 (2), S. 217–226. DOI: 10.1016/0304-3959(94)90097-3.

Price, Donald D.; Finniss, Damien G.; Benedetti, Fabrizio (2008): A comprehensive review of the placebo effect: recent advances and current thought. In: *Annual review of psychology* 59, S. 565–590. DOI: 10.1146/annurev.psych.59.113006.095941.

Rahal, Vanessa; Gallinari, Marjorie O.; Perdigao, Jorge; Cintra, Luciano T. A.; dos Santos, Paulo H.; Briso, Andre L. F. (2015): Quantitative Sensory Testing of the Effect of Desensitizing Treatment After Dental Bleaching. In: *Acta odontologica latinoamericana : AOL* 28 (3), S. 263–270.

Rolke, R.; Baron, R.; Maier, C.; Tölle, T. R.; Treede, R-D; Beyer, A. et al. (2006): Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. In: *Pain* 123 (3), S. 231–243. DOI: 10.1016/j.pain.2006.01.041.

Rothstein, Hannah R. (2006): Publication Bias. In: Samuel Kotz, Campbell B. Read, N. Balakrishnan, Brani Vidakovic und Norman L. Johnson (Hg.): Encyclopedia of statistical sciences, Bd. 17. 2nd ed. Hoboken, N.J.: Wiley-Interscience, S. 1–11.

Rubaai, Ahmed (2012): Our Review Process and Impact Factor [Publications]. In: *IEEE Ind. Appl. Mag.* 18 (6), S. 84. DOI: 10.1109/MIAS.2012.2220495.

Salomons, Tim V.; Iannetti, Gian Domenico; Liang, Meng; Wood, John N. (2016): The "Pain Matrix" in Pain-Free Individuals. In: *JAMA neurology* 73 (6), S. 755–756. DOI: 10.1001/jamaneurol.2016.0653.

Sambo, Chiara F.; Howard, Matthew; Kopelman, Michael; Williams, Steven; Fotopoulou, Aikaterini (2010): Knowing you care: effects of perceived empathy and attachment style on pain perception. In: *Pain* 151 (3), S. 687–693. DOI: 10.1016/j.pain.2010.08.035.

Schiff, Thomas; He, Tao; Sagel, Lisa; Baker, Robert; others (2006): Efficacy and safety of a novel stabilized stannous fluoride and sodium hexametaphosphate dentifrice for dentinal hypersensitivity. In: *J Contemp Dent Pract* 7 (2), S. 1–8. Online verfügbar unter http://www.tidestain.com/media/en-US/research_db/pdf/jcdp/schiffmay06.pdf, zuletzt geprüft am 08.09.2015.

Scholz, Joachim; Woolf, Clifford J. (2002): Can we conquer pain? In: *Nature neuroscience* 5 Suppl, S. 1062–1067. DOI: 10.1038/nn942.

Selinger, Marilyn; Prescott, Thomas E.; Hoffman, Irwin (1994): Temperature acceleration in cold oral stimulation. In: *Dysphagia* 9 (2), S. 83–87. DOI: 10.1007/BF00714591.

Spielberger, Charles D. (2010): State-Trait Anxiety Inventory. In: Irving B. Weiner und W. Edward Craighead (Hg.): The Corsini Encyclopedia of Psychology. Hoboken, NJ, USA: John Wiley & Sons, Inc.

St John Smith, Ewan (2018): Advances in understanding nociception and neuropathic pain. In: *Journal of neurology* 265 (2), S. 231–238. DOI: 10.1007/s00415-017-8641-6.

Sullivan, Michael J. L.; Bishop, Scott R.; Pivik, Jayne (1995a): The Pain Catastrophizing Scale. Development and validation. In: *Psychological Assessment* 7 (4), S. 524–532. DOI: 10.1037/1040-3590.7.4.524.

Sullivan, Michael J. L.; Bishop, Scott R.; Pivik, Jayne (1995b): The Pain Catastrophizing Scale: Development and validation. In: *Psychological Assessment* 7 (4), S. 524–532. DOI: 10.1037/1040-3590.7.4.524.

Sullivan, Michael J.L; Adams, Heather; Sullivan, Maureen E. (2004): Communicative dimensions of pain catastrophizing. Social cueing effects on pain behaviour and coping. In: *Pain* 107 (3), S. 220–226. DOI: 10.1016/j.pain.2003.11.003.

Susser, E.; Sprecher, E.; Yarnitsky, D. (1999): Paradoxical heat sensation in healthy subjects: peripherally conducted by A delta or C fibres? In: *Brain : a journal of neurology* 122 (Pt 2), S. 239–246.

Svensson, P.; Baad-Hansen, L.; Pigg, M.; List, T.; Eliav, E.; Ettlin, D. et al. (2011): Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions--a taskforce report. In: *Journal of Oral Rehabilitation* 38 (5), S. 366–394. DOI: 10.1111/j.1365-2842.2010.02196.x.

Taha, Sahar; Clarkson, Brian H. (Hg.) (2014): Clinician's Guide to the Diagnosis and Management of Tooth Sensitivity. Berlin, Heidelberg, s.l.: Springer Berlin Heidelberg. Online verfügbar unter http://dx.doi.org/10.1007/978-3-642-45164-5.

Tishler, Carl L.; Bartholomae, Suzanne (2002): The recruitment of normal healthy volunteers: a review of the literature on the use of financial incentives. In: *The Journal of Clinical Pharmacology* 42 (4), S. 365–375.

Tracey, Irene (2010): Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. In: *Nature Medicine* 16, 1277 EP -. DOI: 10.1038/nm.2229.

Tracey, Irene; Mantyh, Patrick W. (2007): The cerebral signature for pain perception and its modulation. In: *Neuron* 55 (3), S. 377–391. DOI: 10.1016/j.neuron.2007.07.012.

Vachon-Presseau, E.; Centeno, M. V.; Ren, W.; Berger, S. E.; Tétreault, P.; Ghantous, M. et al. (2016): The Emotional Brain as a Predictor and Amplifier of Chronic Pain. In: *Journal of dental research* 95 (6), S. 605–612. DOI: 10.1177/0022034516638027.

Villemure, Chantal; Bushnell, Catherine M. (2002): Cognitive modulation of pain: how do attention and emotion influence pain processing? In: *Pain* 95 (3), S. 195–199. DOI: 10.1016/S0304-3959(02)00007-6.

Wager, Tor D.; Atlas, Lauren Y.; Lindquist, Martin A.; Roy, Mathieu; Woo, Choong-Wan; Kross, Ethan (2013): An fMRI-based neurologic signature of physical pain. In: *The New England journal of medicine* 368 (15), S. 1388–1397. DOI: 10.1056/NEJMoa1204471.

Williams, Amanda C. de C. (2002): Facial expression of pain, empathy, evolution, and social learning. In: *Behav. Brain Sci.* 25 (04). DOI: 10.1017/S0140525X02430087.

WISE-Onlinesurvey (2016): WISE. Online verfügbar unter http://www.scientific-affairs.ch/limesurvey/index.php/877782?lang=en, zuletzt geprüft am 12.09.2018.

Yarkoni, Tal (2015a): No, the dorsal anterior cingulate is not selective for pain: comment on Lieberman and Eisenberger (2015). Online verfügbar unter http://www.talyarkoni.org/blog/2015/12/05/no-the-dorsal-anterior-cingulate-is-not-selective-for-pain-comment-on-lieberman-and-eisenberger-2015/, zuletzt aktualisiert am 21.09.2018, zuletzt geprüft am 21.09.2018.

Yarkoni, Tal (2015b): Still not selective: comment on comment on comment on Lieberman & Eisenberger (2015). Online verfügbar unter http://www.talyarkoni.org/blog/2015/12/14/still-not-selective-comment-on-comment-on-comment-on-lieberman-eisenberger-2015/?subscribe=success#blog_subscription-2, zuletzt geprüft am 12.09.2018.

Yarkoni, Tal (2018): If we already understood the brain, would we even know it? Online verfügbar unter https://www.talyarkoni.org/blog/2018/08/18/if-we-already-understood-the-brain-would-we-even-know-it/, zuletzt geprüft am 21.09.2018.

3 Summary and general discussion

This synopsis presents three empirical studies that introduce a tool for computer-based pain assessment and the quantification of somatosensory differences between cold air induced painful and non-painful states in the human trigeminal system by means of QST and fMRI. The studies have been extensively discussed in the discussion sections above and are briefly summarized as follows.

Study 1 presents the first freely accessible comprehensive computer-based pain assessment tool, providing data acquisition for both clinic and research based on symptom burden and response-driven case finding (WISE-Onlinesurvey 2016). The patient's response-driven tool includes pain mapping, temporomandibular (TMD) symptoms, severity of somatic symptoms, burden by psychosocial stress, cognitive and emotional representations of illness and health threat, injustice experience due to accidents, injuries or maltreatment, assessment of excessive preoccupation with imagined or actual, minimal defects in appearance that significantly influence psychosocial functioning, Tinnitus handicap and migraine screening. Upon exceeding a predefined checklist threshold value, in-depth items were presented, such as time patterns, location, duration and diurnal pain course.

Hitherto, the majority of somatosensory pain studies on a cortical level have been focussing on the investigation of peripherally transduced and spinally transmitted nociception (Binshtok 2011). Actually, the exploration of trigeminally induced pain has been given more attention in the last decade, but even these studies demonstrated the flaw of lacking external validity of stimuli in some part (vibratory, electrical or air stimuli at room temperature). One example of the importance of stimulus quality and gradeability demonstrates dental tissue: it is known to include – amongst others – cold-specific thermoceptors that are only activated at certain levels of (cold) temperatures.

The studies 2 and 3 intended to overcome the current lack of natural-like, gradable non-contact cold stimuli in the exploration of dental pain by providing data concerning the questions: Firstly, is it possible to develop a technical solution of graded cold air application on human in vivo teeth in MR-environment? And secondly, how reliable is DH perception (trigeminal system) over time after repetitive exposure of tissue to gradable cold air stimuli?

Study 2 presents the development and technical foundation of the world's first application device delivering graded non-contact cold air stimulation in a 3 Tesla-MR environment. Its applicability for brain imaging was successfully demonstrated by showing brain activation changes in typical somatosensory areas such as Cerebellum, Insula, Thalamus, Cingulate cortex, Frontal cortex and Somatosensory cortex.

Study 3 incorporates psychophysical reliability testing of dental perception stability over time (painful vs non-painful states) and shows its challenges and limitations within a subgroup of DH subjects. In particular, the highly volatile intraindividual time course of DH in most subjects presents a great challenge for reliability testing (see study 3, Fig. 3).

These studies present some pioneer work in the investigation of behaviour and neural correlates of painful somatosensory sensation of trigeminal input by use of intraorally applied and focused, gradable cold air stimuli. But their pioneer character should not blind the reader to the fact, that statements about pain processing and experience are not flawless, but rather suffer from diverse crucial shortcomings of single centre studies focusing on isolated aspects of a highly complex issue: the human pain experience.

The following chapters take the liberty to focus on the discussion of i) a critical outlook ii) the fundamental problem of current neuroscientific pain studies and iii) a conclusion including claims for future (neuroscientific) pain research.

3.1 *Outlook*

The three presented studies may be considered as a basis for further implications in both basic and applied research. Study 1 provides a freely available tool of state-of-the-art patient data collection for clinical and diagnostical purposes and for research purposes. The response tailored selection of items allows both a time saving but still thorough exploration of symptom location and symptom burden. Its applicability in every internet supplied spot on the globe with low cost devices such as tablets and its free availability makes it the ideal tool for future multicentre studies and for clinical assessment even in low income countries.

The absolutely novel stimulation procedure by use of the cold air application apparatus CASA (study 2) may not only be used for tooth stimulation, but for human and technical research and material sciences, where gradable cold air stimuli on small areas in restricted space are

needed, even in MR-environment up to 3 Tesla. It thus seems to be expanding the possibilities and applicability of QST, the gold standard of quantification of sensation. One application for future studies might be the comparison of sensory thresholds on different human body parts for comparison with dental perception and the comparison to current QST parameters.

Up to now, no standardized assessment tools are available for objective measures of temperature sensitive DH. Study 3 lays the foundation on one hand for basic QST research and on the other hand for the standardized evaluation of intervention studies in DH, including reliability testing with a reduced examiner effect due to the stimulus application setting, which makes CASA unique.

CASA with its MR-compatibility and its demonstrated applicability in psychophysical assessment in painless and painful states lays the foundation for neuroscientific investigation and imaging. This may allow a deeper insight in processes of spinal and supraspinal pain processing.

Brain imaging data provided by CASA-stimulated subjects are suitable for up to date statistical analyses which revolutionize the 'traditional' forward inference methods: The analysis of fMR-data was performed by use of statistical methods, that draw a conclusion from differences between mental states (e.g. painful vs. non-painful) or co-registered variables (e.g. questionnaires): This method - called *forward inference* (Fig. 1) - strives to find relevant correlations between oxygenation level changes in CNS-tissue and predefined states (Ogawa et al. 1990).

Based on forward inference statistics, early neuroscientific findings in pain research assume the existence of a pain matrix (Peyron et al. 2000), a brain network especially sensitive for pain sensation. This assumption has come under scrutiny within the last decade and still waits for verification: Similar network activation changes were observed within congenitally analgesic subjects (Salomons et al. 2016) and in non-painful stimulation conditions (Legrain et al. 2011). Up to now, no brain area or network is known to be pain specific.

New methodological approaches try to approach the question of a 'neural pain signature' by putting the cart before the horse: By use of machine-learning, algorithms analysing brain activation changes are used to infer that pain perception occurred, thus called *reverse inference*

(Wager et al. 2013; Gruss et al. 2015; Lieberman und Eisenberger 2015). This is one more approach in the quest of the holy grail of *pain specificity* in the CNS.

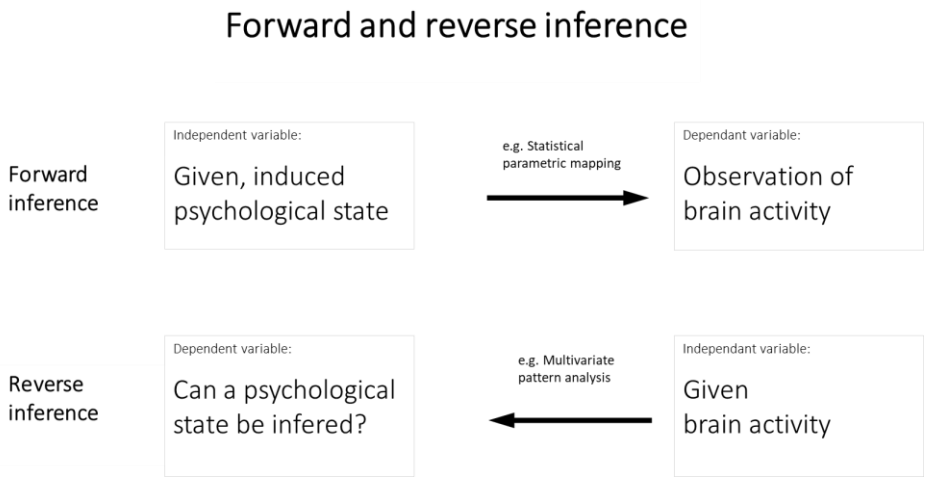

Fig. 1: Schematic of forward and reverse inference.

This quest recently experienced some setbacks because of methodological issues (Yarkoni 2015a, 2015b; Poldrack 2006) and interpretational issues (Poldrack 2006; Hu und Iannetti 2016; Salomons et al. 2016): Up to now, no neural pain marker is known and currently there exists no other plan to answer this question than by segmented non-coordinated research projects spread over the globe without any consensus of mandatory principles of pain studies and mainly by use of neuroinformatics. Furthermore, the meaningfulness of the search of pain specificity is not questioned in current neuroscientific studies. Against this background, some fundamental reflections follow.

3.2 *Fundamental problems of the scientific study of pain*

It is suffering, not pain, that brings patients into doctor's offices in hopes of finding relief.

J. D. Loeser

3.2.1 Problem 1: Semantic simplification of a highly complex and interdependent phenomenon

The first challenge in the neuroscientific study of pain is the singularity of the notion 'pain', trying to outline one of the phylogenetically oldest motivational systems: pain (definition see Introduction). It pretends to be a well outlined entity. Most of the pain studies talk about *the pain* like a duck takes the water; it is very arguable whether the use of this single term is sufficient as a basis to draw reliable conclusions about the genesis of a phylogenetic crucial sensory modality of the human being. Although the IASP make a thorough definition of pain (see introduction), the extended features of the pain definition are neglected in most pain studies. For further differentiation of the term 'pain', amongst other questionnaires, the McGill pain questionnaire (Melzack 1975b) tries to elucidate some more aspects of the pain experience. Spatial, temporal, sensory-specific, affective and evaluative descriptors are introduced in order to differentiate the single notion pain and in a further step make statements about different methods to relieve pain. This linguistic approach to differentiate the concept *pain* is to be replenished by other crucial aspects (list incomplete):

- Gender differences (Paulson et al. 1998)
- Age differences, controllability of pain (Bräscher et al. 2016)
- Social aspects in acute and chronic pain conditions (Kröner-Herwig 2014)
- Expectation in placebo conditions (Price et al. 2008; Tracey 2010; Colloca und Benedetti 2007)
- Anticipation (Ploghaus 1999)
- Examiner effect (Kállai et al. 2004; Ohrbach et al. 1998)
- Emotional states (Craig 2003; Villemure und Bushnell 2002; Vachon-Presseau et al. 2016; Baliki und Apkarian 2015)
- Hormone levels and allostatic load (McEwen 2008, 1998)
- Molecular and physiological processes
- Genetical features

- The individual's idiosyncracy of acceptance of pain vs fighting against pain (McCracken et al. 2004).
- The individual's self-regulation capabilities (Higgins 1997)
- The individual's cognitive biases such as catastrophization (Sullivan et al. 1995b; Colloca und Benedetti 2007)
- Incentive: paid (e.g. in academic studies) vs not-paid pain study participation.
- Self-selection bias: Subjects - fortunately – cannot be forced to participate in scientific studies (https://www.swissethics.ch/gesetzrichtl.html). As simple as it sounds as crucial it is: Pain, fear and avoidance are highly correlated, thus self selection bias systematically excludes the gathering of highly relevant data. This hurdle cannot be cleared in an enlightened civilization.
- The consent and the intensity: All ethically approved scientific studies include the subject's informed consent, allow the subjects to stop their participation anytime and to control the intensity and duration of experimental pain stimuli. As mentioned above, cognitive and emotional states do highly bias pain experience.
- Relevant biographical events: Pain and nociception is not only assumed to be a *nature* problem, but also a question of *nurture* (Belfer 2013). Pain experience history seems indispensable for ideographic data gathering (which lays foundation of nomothetic data).
- Consistency: Is pain an interindividual consistent concept? How reliable is it over time?
- Specificity vs sensitivity: Is it appropriate to extrapolate from data or image to pain (Blankenbaker et al. 2008)?
- Social desirability response bias (Logan et al. 2008)

This listing surely can be continued by many other crucial aspects of the study of pain processing and experience.

It tries to demonstrate that for research purposes the single notion 'pain' imperatively needs to be specified by further definitions or declaration of limitations.

An example for clarification: While screening potential subjects for inclusion criteria, the author of this thesis observed, that some of the subjects reported pain (on a pain scale and by observing physiognomic reactions) after cold air stimulation. Immediate consecutive verbal interrogation by the examiner revealed, that the subjects were capable of differentiating the

sensory experience; statements like *'well, it was intense, but not really painful'*, *'I was scared of upcoming excruciating pain'* (this subject reported pain before onset of stimulation) or *'that was very painful, but no problem, go on'*. This spontaneous narrative approach during screening was not controlled for but out of the author's perspective seems to be very important for neuroscientific approaches: pain is not only a standard experience, it's a multifaceted result of interpretation and estimation. And the latter take place in the CNS. And for the sensory and integrating CNS processes the author assumes generally: *Nothing exists that doesn't matter to the CNS*. Can, for instance any pain study be valid without a profound and precise control of the subject's anticipation effects?
Summarising, some effects like loss of control, social desirability, fear and uncertainty are very often excluded in pain research, although they significantly affect pain experience. The neglect of these and other relevant aspects massively narrows the validity of scientific statements about the single notion 'pain'. This leads to problem No. 2.

3.2.2 Problem 2: Reckless simplification by methodological neglect

"Dert äne isch es donku wie ire Chue, hie hani wenigschtens ächli Liecht."
('Back there it's as dark as inside a cow, here at least it is bright enough.')

Dällebach Kari, well-known swiss character

This citation in Swiss-german is attributed to a well-known swiss character who lived in the Swiss capital Bern in the early 1900s. At night time, searching for a key in the cone of light of a street lamp he was asked where about he had lost his key. Pointing back into the dark he uttered: 'Back there. But there it's as dark as inside a cow, here at least it is bright enough.' Dällebach certainly tried to do his best in finding his key. But, restricted field of focus of a technical device (streetlamp) mislead Dällebach, alienating him from his initial goal. Concluding, the use of methods, for instance fMRI, should carefully be reflected whether they really meet the relevant research questions or whether their elaborated technical power simply deceive the researcher.

To some extent, simplification of complex relations is an indispensable method of many sciences. But, concerning the scientific investigation of the pain experience, the applied simplification in the fields of current neuroscientific research is overshooting the mark - or rather *undershooting* the mark. Reckless simplification in this context says, that to many crucial aspects

in pain studies are only selectively taken into consideration thus invalidating results, see problem 1.

Reckless simplification is not only presumed by the use of one single and insufficiently defined word (‘pain’) for a complex sensory or endogenous phenomenon. But also, the use of one or a very small number of methods at a time and study designs mostly focus on a very narrow range of variables neglecting many other highly crucial methodological and interpretational aspects (Yarkoni 2018). Definition of neuroscientific pain research questions are mostly tailored to one single method (e.g. blood oxygenation level dependent (BOLD)-response in the current study 2).

Possible reasons may be found for one thing in pragmatic limitations of projects: the simultaneous implementation of different methodological approaches is not only demanding in terms of expenditure of examination time per subject but also by financial limitations. If a neuroscientific study would be complemented by the collection of genetic, molecular and behaviour data and medical history (of subjects and their relatives) the financial expenditure would exceed the capacity of most grants or lead to small subject numbers.

Further on, a serious limitation consists of the structural flaws of the incentive system in science: In the middle ages, for decision making often one observation was sufficent (e.g. for trial by ordeal). Nowadays it can be assumed, we need more than one timepoint of data collection to make reliable, trustworthy statements, for instance about pain processing in humans. In the current scientific community there is little incentive to pursue this goal, because of the main short term incentive of numerous peer reviewed publications and the pressure of the expected novelty effect in studies (Harzing Anne-Wil 2017; Gneezy et al. 2011). This short - or at the best - middle-term incentive narrows profound pain research and fosters fast data output at the expense of reliable long-term data (Brembs 2018; Naranayan 1985; Gneezy et al. 2011).
In addition, publication bias (Rothstein 2006; Baker und Jackson 2006) and impact factor bias (Rubaai 2012), as in many scientific fields, is under scrutiny (Newcombe und Bouton 2009; Elsevier und Franklin 2018).

4 Conclusion and claim

This thesis presents some pioneer work in open source, computer-aided pain assessment considering the bio-psycho-social perspective, in vivo MR-compatible dental cold air stimulation and longitudinal trigeminal QST. In the future, these methods and data may further be applied both in clinical and research settings for basic research or applied cross-sectional and longitudinal studies and even in material sciences.

The author's experiences during data acquisition and analysis led to reflections about (neuroscientific) pain research: Limitations and flaws in the above presented original experimental research projects lay the foundations for epistemological reflections for future pain research. Herewith, six claims for future neuroscientific pain studies are concluded:

1. Hitherto, the IASPs thorough pain definition is only considered in part in current pain studies: This partial neglect is inacceptable. The consideration of the comprehensive IASP pain definition and an international consensus of minimal requirements of pain state assessment in neuroscience is to be aimed at. The use of the uncommented single term pain in research is inacceptable regarding its highly volatile and interdependent emergence and its vast complexity.
   International mandatory requirements for neuroscientific pain research should be discussed and defined, analogue to guidelines for clinical pain assessment and treatment: What variables should be controlled for mandatorily or be declared why they were neglected.
2. Stop treating academic science as a competition-driven market, that strives for a maximal fraction of findings in order to achieve a maximum of publications. This incentive is not expedient regarding intrinsically motivated in-depth science.
3. Prevent wild west (first shoot, then ask): Peer-reviewed methodological pre-hoc discussion of study designs is needed and should have priority over fast post-hoc data output. Thereby, more valid outcomes in a more resource-saving way can be expected.
4. Nociception (physiological process) can be considered as *syntax*, whereas pain can be considered as the *semantics*, which adds *meaning* to basic processes. The latter rises the degree of freedom, complicating a consequent and coherent of a neuroscientific

approach to pain. Is the quest of the holy grail ‘pain specificity’ in the CNS adequate? Talk about relevant future aims and meaningfulness of pain studies with respect to long term purposes, considering the multifaceted aspects of this sensory phenomenon in toto.

5. Optimize resource allocation: Less mono-disciplinary, more multi-disciplinary pain studies are needed. Aggregation of knowledge, financial and technical resources is to be achieved, ideally in multi-center settings in order to enhance validity of statements about the notion pain.
6. Leave the middle ages and aim at reliability: We need more than one observation to draw conclusions. Stop novelty pressure for a while and strive for reflection by use of replication: Other incentives than *novelty* and *publication pressure* (see No. 2) should be established by both sponsors and researchers. Alternative publication processes are needed for a more valid approach of the notion pain.

5 Contribution of the author

Study 1: intellectual contributions to the content.

Studies 2 and 3: Technical development and construction of MR-compatible cold air stimulation device, recruitment, operation cold air stimulator CASA during MR-measurement, subject management, QST reliability measurements, statistical analysis, writing.

This thesis was written by me and in my own words, except for quotations from published and unpublished sources which are clearly indicated and acknowledged as such.

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7 References

Alvarado, Lisa T.; Perry, Griffin M.; Hargreaves, Kenneth M.; Henry, Michael A. (2007): TRPM8 Axonal expression is decreased in painful human teeth with irreversible pulpitis and cold hyperalgesia. In: *Journal of endodontics* 33 (10), S. 1167–1171. DOI: 10.1016/j.joen.2007.06.018.

Anand, K. J. S.; Hall, R. Whit (2007): Controversies in neonatal pain: an introduction. In: *Seminars in perinatology* 31 (5), S. 273–274. DOI: 10.1053/j.semperi.2007.07.014.

Apkarian, A. Vania; Bushnell, M. Catherine; Treede, Rolf-Detlef; Zubieta, Jon-Kar (2005): Human brain mechanisms of pain perception and regulation in health and disease. In: *European journal of pain (London, England)* 9 (4), S. 463–484. DOI: 10.1016/j.ejpain.2004.11.001.

Apkarian, A. Vania; Stea, Richard A.; Bolanowski, Stanley J. (2009): Heat-Induced Pain Diminishes Vibrotactile Perception. A Touch Gate. In: *Somatosensory & Motor Research* 11 (3), S. 259–267. DOI: 10.3109/08990229409051393.

AWMF (1962/2018): AWMF: Leitlinien-Suche. Online verfügbar unter https://www.awmf.org/leitlinien/leitlinien-suche.html, zuletzt geprüft am 10.08.2018.

Backonja, Miroslav Misha; Attal, Nadine; Baron, Ralf; Bouhassira, Didier; Drangholt, Mark; Dyck, Peter J. et al. (2013): Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. In: *Pain* 154 (9), S. 1807–1819. DOI: 10.1016/j.pain.2013.05.047.

Baker, Rose; Jackson, Dan (2006): Using journal impact factors to correct for the publication bias of medical studies. In: *Biometrics* 62 (3), S. 785–792. DOI: 10.1111/j.1541-0420.2005.00513.x.

Baliki, Marwan N.; Apkarian, A. Vania (2015): Nociception, Pain, Negative Moods, and Behavior Selection. In: *Neuron* 87 (3), S. 474–491. DOI: 10.1016/j.neuron.2015.06.005.

Bartold, P. M. (2006): Dentinal hypersensitivity. A review. In: *Australian Dental Journal* 51 (3), S. 212–218. DOI: 10.1111/j.1834-7819.2006.tb00431.x.

Basbaum, Allan I.; Bautista, Diana M.; Scherrer, Grégory; Julius, David (2009): Cellular and molecular mechanisms of pain. In: *Cell* 139 (2), S. 267–284. DOI: 10.1016/j.cell.2009.09.028.

Belfer, Inna (2013): Nature and nurture of human pain. In: *Scientifica* 2013, S. 415279. DOI: 10.1155/2013/415279.

Binshtok, Alexander M. (2011): Mechanisms of nociceptive transduction and transmission: a machinery for pain sensation and tools for selective analgesia. In: *International review of neurobiology* 97, S. 143–177. DOI: 10.1016/B978-0-12-385198-7.00006-0.

Blankenbaker, Donna G.; Ullrick, Steven R.; Davis, Kirkland W.; Smet, Arthur A. de; Haaland, Ben; Fine, Jason P. (2008): Correlation of MRI findings with clinical findings of trochanteric pain syndrome. In: *Skeletal radiology* 37 (10), S. 903–909. DOI: 10.1007/s00256-008-0514-8.

Bräscher, Anne-Kathrin; Becker, Susanne; Hoeppli, Marie-Eve; Schweinhardt, Petra (2016): Different Brain Circuitries Mediating Controllable and Uncontrollable Pain. In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 36 (18), S. 5013–5025. DOI: 10.1523/JNEUROSCI.1954-15.2016.

Brembs, Björn (2018): Prestigious Science Journals Struggle to Reach Even Average Reliability. In: *Frontiers in human neuroscience* 12, S. 37. DOI: 10.3389/fnhum.2018.00037.

Brügger, M.; Lutz, K.; Brönnimann, B.; Meier, M. L.; Luechinger, R.; Barlow, A. et al. (2012): Tracing toothache intensity in the brain. In: *Journal of dental research* 91 (2), S. 156–160. DOI: 10.1177/0022034511431253.

Brügger, Mike; Ettlin, Dominik A.; Meier, Michael; Keller, Thierry; Luechinger, Roger; Barlow, Ashley et al. (2011): Taking Sides with Pain - Lateralization aspects Related to Cerebral Processing of Dental Pain. In: *Frontiers in human neuroscience* 5, S. 12. DOI: 10.3389/fnhum.2011.00012.

Colloca, Luana; Benedetti, Fabrizio (2007): Nocebo hyperalgesia: how anxiety is turned into pain. In: *Current opinion in anaesthesiology* 20 (5), S. 435–439. DOI: 10.1097/ACO.0b013e3282b972fb.

Craig, A. D. (2002): How do you feel? Interoception: the sense of the physiological condition of the body. In: *Nature reviews. Neuroscience* 3 (8), S. 655–666. DOI: 10.1038/nrn894.

Craig, A. D. (2003): A new view of pain as a homeostatic emotion. In: *Trends in neurosciences* 26 (6), S. 303–307.

Dababneh, R. H.; Khouri, A. T.; Addy, M. (1999): dentine hypersensitivity. Dentine hypersensitivity — an enigma? a review of terminology, mechanisms, aetiology and management. In: *Br Dent J* 187 (11), S. 606–611. DOI: 10.1038/sj.bdj.4800345.

DaSilva, Alex F. M.; Becerra, Lino; Makris, Nikos; Strassman, Andrew M.; Gonzalez, R. Gilberto; Geatrakis, Nina; Borsook, David (2002): Somatotopic activation in the human trigeminal pain pathway. In: *The Journal of neuroscience : the official journal of the Society for Neuroscience* 22 (18), S. 8183–8192.

Elsevier; Franklin, Jennifer (2018): Results masked review: peer review without publication bias. Online verfügbar unter https://www.elsevier.com/connect/reviewers-update/results-masked-review-peer-review-without-publication-bias, zuletzt aktualisiert am 11.09.2018, zuletzt geprüft am 12.09.2018.

Ettlin, D. A.; Brügger, M.; Keller, T.; Luechinger, R.; Jäncke, L.; Palla, S. et al. (2009): Interindividual differences in the perception of dental stimulation and related brain activity. In: *European journal of oral sciences* 117 (1), S. 27–33. DOI: 10.1111/j.1600-0722.2008.00590.x.

Ettlin, D. A.; Zhang, H.; Lutz, K.; Järmann, T.; Meier, D.; Gallo, L. M. et al. (2004): Cortical activation resulting from painless vibrotactile dental stimulation measured by functional magnetic resonance imaging (FMRI). In: *Journal of dental research* 83 (10), S. 757–761. DOI: 10.1177/154405910408301004.

Ferrari, Marco; Quaresima, Valentina (2012): A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. In: *NeuroImage* 63 (2), S. 921–935. DOI: 10.1016/j.neuroimage.2012.03.049.

Garcia-Larrea, Luis; Peyron, Roland (2013): Pain matrices and neuropathic pain matrices: a review. In: *Pain* 154 Suppl 1, S29-43. DOI: 10.1016/j.pain.2013.09.001.

Gneezy, Uri; Meier, Stephan; Rey-Biel, Pedro (2011): When and Why Incentives (Don't) Work to Modify Behavior. In: *Journal of Economic Perspectives* 25 (4), S. 191–210. DOI: 10.1257/jep.25.4.191.

Gruss, Sascha; Treister, Roi; Werner, Philipp; Traue, Harald C.; Crawcour, Stephen; Andrade, Adriano; Walter, Steffen (2015): Pain Intensity Recognition Rates via Biopotential Feature Patterns with Support Vector Machines. In: *PloS one* 10 (10), e0140330. DOI: 10.1371/journal.pone.0140330.

Harzing Anne-Wil (2017): Publish or Perish: Realising Google Scholar’s potential to democratise citation analysis. https://harzing.com/download/gsday_madrid.pdf. Online verfügbar unter https://harzing.com/download/gsday_madrid.pdf, zuletzt geprüft am 19.09.2018.

Higgins, E. Tory (1997): Beyond pleasure and pain. In: *American Psychologist* 52 (12), S. 1280–1300. DOI: 10.1037/0003-066X.52.12.1280.

Hu, Li; Iannetti, Gian Domenico (2016): Painful Issues in Pain Prediction. In: *Trends in neurosciences* 39 (4), S. 212–220. DOI: 10.1016/j.tins.2016.01.004.

IASP (1994): IASP Terminology - IASP. Online verfügbar unter http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Pain, zuletzt aktualisiert am 2017, zuletzt geprüft am 19.09.2018.

Johnston, Mary E. (1994): Effects of Computer-based Clinical Decision Support Systems on Clinician Performance and Patient Outcome: A Critical Appraisal of Research. In: *Ann Intern Med* 120 (2), S. 135. DOI: 10.7326/0003-4819-120-2-199401150-00007.

Kállai, Ibolya; Barke, Antonia; Voss, Ursula (2004): The effects of experimenter characteristics on pain reports in women and men. In: *Pain* 112 (1-2), S. 142–147. DOI: 10.1016/j.pain.2004.08.008.

Kim, Yun Sook; Park, Jun Hong; Choi, Su Jung; Bae, Jin Young; Ahn, Dong Kuk; McKemy, David D.; Bae, Yong Chul (2014): Central connectivity of transient receptor potential melastatin 8-expressing axons in the brain stem and spinal dorsal horn. In: *PloS one* 9 (4), e94080. DOI: 10.1371/journal.pone.0094080.

Kröner-Herwig, B. (2014): Einfluss von kognitiv-emotionalen Prozessen auf Schmerz und Funktionsbeeinträchtigung. Eine psychobiologische Perspektive. In: *Schmerz (Berlin, Germany)* 28 (5), 537-44; quiz 545-6. DOI: 10.1007/s00482-014-1468-5.

Kuijpers, T.; van Middelkoop, M.; Rubinstein, S. M.; Ostelo, R.; Verhagen, A.; Koes, B. W.; van Tulder, M. W. (2011): A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. In: *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 20 (1), S. 40–50. DOI: 10.1007/s00586-010-1541-4.

Legrain, Valéry; Iannetti, Gian Domenico; Plaghki, Léon; Mouraux, André (2011): The pain matrix reloaded: a salience detection system for the body. In: *Progress in Neurobiology* 93 (1), S. 111–124. DOI: 10.1016/j.pneurobio.2010.10.005.

Lieberman, Matthew D.; Eisenberger, Naomi I. (2015): The dorsal anterior cingulate cortex is selective for pain: Results from large-scale reverse inference. In: *Proceedings of the National*

Academy of Sciences of the United States of America 112 (49), S. 15250–15255. DOI: 10.1073/pnas.1515083112.

Logan, Deirdre E.; Claar, Robyn Lewis; Scharff, Lisa (2008): Social desirability response bias and self-report of psychological distress in pediatric chronic pain patients. In: *Pain* 136 (3), S. 366–372. DOI: 10.1016/j.pain.2007.07.015.

McCracken, Lance M.; Vowles, Kevin E.; Eccleston, Christopher (2004): Acceptance of chronic pain: component analysis and a revised assessment method. In: *Pain* 107 (1), S. 159–166. DOI: 10.1016/j.pain.2003.10.012.

McEwen, Bruce S. (1998): Stress, Adaptation, and Disease: Allostasis and Allostatic Load. In: *Annals of the New York Academy of Sciences* 840 (1), S. 33–44. DOI: 10.1111/j.1749-6632.1998.tb09546.x.

McEwen, Bruce S. (2008): Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. In: *European journal of pharmacology* 583 (2-3), S. 174–185. DOI: 10.1016/j.ejphar.2007.11.071.

Meier, Michael L.; Brügger, Michael; Ettlin, Dominik A.; Luechinger, Roger; Barlow, Ashley; Jäncke, Lutz; Lutz, Kai (2012): Brain activation induced by dentine hypersensitivity pain--an fMRI study. In: *Journal of clinical periodontology* 39 (5), S. 441–447. DOI: 10.1111/j.1600-051X.2012.01863.x.

Melzack, R.; Wall, P. D. (1965): Pain Mechanisms. A New Theory. In: *Science* 150 (3699), S. 971–978. DOI: 10.1126/science.150.3699.971.

Melzack, Ronald (1975): The McGill Pain Questionnaire: Major properties and scoring methods. In: *Pain* 1 (3), S. 277–299. DOI: 10.1016/0304-3959(75)90044-5.

Millan, Mark J. (1999): The induction of pain: an integrative review. In: *Progress in Neurobiology* 57 (1), S. 1–164. DOI: 10.1016/S0301-0082(98)00048-3.

Mogil, Jeffrey S. (2012): Pain genetics: past, present and future. In: *Trends in genetics : TIG* 28 (6), S. 258–266. DOI: 10.1016/j.tig.2012.02.004.

Morley, Stephen; Eccleston, Christopher; Williams, Amanda (1999): Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour

therapy for chronic pain in adults, excluding headache. In: *Pain* 80 (1), S. 1–13. DOI: 10.1016/S0304-3959(98)00255-3.

Morley, Stephen; Williams, Amanda (2015): New Developments in the Psychological Management of Chronic Pain. In: *Canadian journal of psychiatry. Revue canadienne de psychiatrie* 60 (4), S. 168–175. DOI: 10.1177/070674371506000403.

Naranayan, M. P. (1985): Managerial Incentives for Short-term Results. In: *The Journal of Finance* 40 (5), S. 1469–1484. DOI: 10.1111/j.1540-6261.1985.tb02395.x.

Nevin, John A. (1969): Signal detection theory and operant behaviorA review of David M. Green and John A. Swets' Signal detection theory and psychophysics1. In: *J Exp Anal Behav* 12 (3), S. 475–480. DOI: 10.1901/jeab.1969.12-475.

Newcombe, Nora S.; Bouton, Mark E. (2009): Masked Reviews Are Not Fairer Reviews: SAGE PublicationsSage CA: Los Angeles, CA. Online verfügbar unter http://journals.sagepub.com/doi/abs/10.1111/j.1745-6924.2009.01102.x, zuletzt aktualisiert am 01.01.2009, zuletzt geprüft am 26.08.2018.

NICE guidelines (1999/2018): Search Results. NICE. Online verfügbar unter https://www.nice.org.uk/search?q=pain, zuletzt geprüft am 10.08.2018.

Noseda, Rodrigo; Burstein, Rami (2013): Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. In: *Pain* 154, S44-S53. DOI: 10.1016/j.pain.2013.07.021.

Ogawa, S.; Lee, T. M.; Kay, A. R.; Tank, D. W. (1990): Brain magnetic resonance imaging with contrast dependent on blood oxygenation. In: *Proceedings of the National Academy of Sciences* 87 (24), S. 9868–9872. DOI: 10.1073/pnas.87.24.9868.

Ohrbach, Richard; Crow, Heidi; Kamer, Angela (1998): Examiner expectancy effects in the measurement of pressure pain thresholds. In: *Pain* 74 (2), S. 163–170. DOI: 10.1016/S0304-3959(97)00174-7.

Paulson, Pamela E.; Minoshima, Satoshi; Morrow, Thomas J.; Casey, Kenneth L. (1998): Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. In: *Pain* 76 (1), S. 223–229. DOI: 10.1016/S0304-3959(98)00048-7.

Peyron, R.; Laurent, B.; García-Larrea, L. (2000): Functional imaging of brain responses to pain. A review and meta-analysis (2000). In: *Neurophysiologie Clinique/Clinical Neurophysiology* 30 (5), S. 263–288. DOI: 10.1016/S0987-7053(00)00227-6.

Ploghaus, A. (1999): Dissociating Pain from Its Anticipation in the Human Brain. In: *Science* 284 (5422), S. 1979–1981. DOI: 10.1126/science.284.5422.1979.

Poldrack, Russell A. (2006): Can cognitive processes be inferred from neuroimaging data? In: *Trends in cognitive sciences* 10 (2), S. 59–63. DOI: 10.1016/j.tics.2005.12.004.

Price, Donald D.; Bush, Francis M.; Long, Stephen; Harkins, Stephen W. (1994): A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. In: *Pain* 56 (2), S. 217–226. DOI: 10.1016/0304-3959(94)90097-3.

Price, Donald D.; Finniss, Damien G.; Benedetti, Fabrizio (2008): A comprehensive review of the placebo effect: recent advances and current thought. In: *Annual review of psychology* 59, S. 565–590. DOI: 10.1146/annurev.psych.59.113006.095941.

Rolke, R.; Baron, R.; Maier, C.; Tölle, T. R.; Treede, R-D; Beyer, A. et al. (2006): Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. In: *Pain* 123 (3), S. 231–243. DOI: 10.1016/j.pain.2006.01.041.

Rothstein, Hannah R. (2006): Publication Bias. In: Samuel Kotz, Campbell B. Read, N. Balakrishnan, Brani Vidakovic und Norman L. Johnson (Hg.): Encyclopedia of statistical sciences, Bd. 17. 2nd ed. Hoboken, N.J.: Wiley-Interscience, S. 1–11.

Rubaai, Ahmed (2012): Our Review Process and Impact Factor [Publications]. In: *IEEE Ind. Appl. Mag.* 18 (6), S. 84. DOI: 10.1109/MIAS.2012.2220495.

Salomons, Tim V.; Iannetti, Gian Domenico; Liang, Meng; Wood, John N. (2016): The "Pain Matrix" in Pain-Free Individuals. In: *JAMA neurology* 73 (6), S. 755–756. DOI: 10.1001/jamaneurol.2016.0653.

Scholz, Joachim; Woolf, Clifford J. (2002): Can we conquer pain? In: *Nature neuroscience* 5 Suppl, S. 1062–1067. DOI: 10.1038/nn942.

St John Smith, Ewan (2018): Advances in understanding nociception and neuropathic pain. In: *Journal of neurology* 265 (2), S. 231–238. DOI: 10.1007/s00415-017-8641-6.

Sullivan, Michael J. L.; Bishop, Scott R.; Pivik, Jayne (1995): The Pain Catastrophizing Scale: Development and validation. In: *Psychological Assessment* 7 (4), S. 524–532. DOI: 10.1037/1040-3590.7.4.524.

Taha, Sahar; Clarkson, Brian H. (Hg.) (2014): Clinician's Guide to the Diagnosis and Management of Tooth Sensitivity. Berlin, Heidelberg, s.l.: Springer Berlin Heidelberg. Online verfügbar unter http://dx.doi.org/10.1007/978-3-642-45164-5.

Tracey, Irene (2010): Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. In: *Nature Medicine* 16, 1277 EP -. DOI: 10.1038/nm.2229.

Tracey, Irene; Mantyh, Patrick W. (2007): The cerebral signature for pain perception and its modulation. In: *Neuron* 55 (3), S. 377–391. DOI: 10.1016/j.neuron.2007.07.012.

Vachon-Presseau, E.; Centeno, M. V.; Ren, W.; Berger, S. E.; Tétreault, P.; Ghantous, M. et al. (2016): The Emotional Brain as a Predictor and Amplifier of Chronic Pain. In: *Journal of dental research* 95 (6), S. 605–612. DOI: 10.1177/0022034516638027.

Villemure, Chantal; Bushnell, Catherine M. (2002): Cognitive modulation of pain: how do attention and emotion influence pain processing? In: *Pain* 95 (3), S. 195–199. DOI: 10.1016/S0304-3959(02)00007-6.

Wager, Tor D.; Atlas, Lauren Y.; Lindquist, Martin A.; Roy, Mathieu; Woo, Choong-Wan; Kross, Ethan (2013): An fMRI-based neurologic signature of physical pain. In: *The New England journal of medicine* 368 (15), S. 1388–1397. DOI: 10.1056/NEJMoa1204471.

WISE-Onlinesurvey (2016): WISE. Online verfügbar unter http://www.scientific-affairs.ch/limesurvey/index.php/877782?lang=en, zuletzt geprüft am 12.09.2018.

Yarkoni, Tal (2015a): No, the dorsal anterior cingulate is not selective for pain: comment on Lieberman and Eisenberger (2015). Online verfügbar unter http://www.talyarkoni.org/blog/2015/12/05/no-the-dorsal-anterior-cingulate-is-not-selective-for-pain-comment-on-lieberman-and-eisenberger-2015/, zuletzt aktualisiert am 21.09.2018, zuletzt geprüft am 21.09.2018.

Yarkoni, Tal (2015b): Still not selective: comment on comment on comment on Lieberman & Eisenberger (2015). Online verfügbar unter http://www.talyarkoni.org/blog/2015/12/14/still-not-selective-comment-on-comment-on-comment-on-lieberman-eisenberger-2015/?subscribe=success#blog_subscription-2, zuletzt geprüft am 12.09.2018.

Yarkoni, Tal (2018): If we already understood the brain, would we even know it? Online verfügbar unter https://www.talyarkoni.org/blog/2018/08/18/if-we-already-understood-the-brain-would-we-even-know-it/, zuletzt geprüft am 21.09.2018.